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Assessing the factors associated with mortality among patients recruited to the PLACID Trial (A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease)

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Assessing the factors associated with mortality among patients recruited to the PLACID Trial (A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease)

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PLACID TRIAL Mortality Assessment

Abstract

Objective:

Large data on the clinical characteristics and outcome of COVID-19 in the Indian population is scarce. We analyzed the factors associated with mortality in a cohort of moderately ill COVID-19 patients enrolled in a randomized trial on convalescent plasma.

Setting:

39 public and private hospitals across India.

Participants:

Of the 464 patients recruited, two were lost to follow-up, nine withdrew consent and two patients did not receive the intervention after randomization. The cohort of 451 participants with known outcome at 28-days were analyzed.

Primary outcome measure:

Factors associated with all-cause mortality at 28 days post-enrolment.

Results:

The mean (SD) age of was 51±12·4 years; 76·7% were male. Admission SOFA score was 2·4±1·1. Non-invasive ventilation, invasive ventilation and vasopressor therapy were required in 98·9%, 8·4% and 4·0% respectively. The 28-day mortality was 14·4%. Median time from symptom onset to hospital admission was similar (p=1.0) in survivors (4 days; IQR 3-7) and non survivors (4 days; IQR 3-6). Patients with two or more co-morbidities had 2·25 (95%CI:1·17–4·32, p=0·014) times risk of death. When compared with survivors, admission IL-6 levels were higher (p<0.001) in non-survivors and increased further on Day 3. On multivariable regression analysis, severity of illness (HR 1·21, 95%CI:1·07-1·36, p=0·002), PaO_2/FiO_2 ratio <100 (3·37, 1·54-7·41, p=0·002), Neutrophil Lymphocyte ratio (NLR) >10 (9·38, 3·67-24·0, p<0·001), D-dimer >1·0mg/l (2·51,1·14-5·51, p=0·022), ferritin >500ng/ml (2·66, 1·46-4·85, p=0·001) and LDH ≥450 IU/L (2·96, 1·61-5·45, p=0·001) were significantly associated with death.

Conclusion:

In this cohort of moderately ill COVID-19 patients, severity of illness, underlying co-morbidities and higher levels of inflammatory markers were significantly associated with death.

Trial Registration:

The trial protocol was registered with the Clinical Trial Registry of India (CTRI/2020/04/024775).

Article Summary

Strengths and limitations of this study

Strengths

There is no study from India, with representation from multiple states that has detailed the clinical profile and evaluated for factors associated with death. This study may help with strategic planning at a national level.

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the present analysis need not be adjusted for convalescent plasma intervention.

There may be variability of treatment provided in the multiple centres, however, care was taken that patients received best standard of care for covid-19 dictated by the best available evidence at the time and guidelines for the management of covid-19 issued by health authorities of the Indian government.

Limitations

The laboratory and biomarker assays for ferritin, lactate dehydrogenase, C reactive protein, and D-dimer were conducted using tests from different manufacturers.

Participants of this study may not comprise a true observational cohort as this was a post hoc analysis of a randomized control trial data and extrapolation to the general population must be carefully qualified.

PLACID TRIAL Mortality Assessment

Introduction:

The first human case of Corona Virus Disease 19 (COVID-19) caused by the novel coronavirus (named Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) was reported in Wuhan City, China in December 2019. On 30 January 2020, the World Health Organization (WHO) declared that the outbreak of COVID-19 constituted a Public Health Emergency of International Concern (1). Based on the high levels of global spread and the severity of COVID-19, on 11 March 2020, the Director-General of the WHO declared the COVID-19 outbreak a pandemic (2). The sudden outbreak followed by rapid spread in a globalized world, resulted in a major medical burden, besides affecting socio-economic wellbeing among all nations.

In India, the disease was first detected on 30 January 2020 in the state of Kerala, in a student who returned from Wuhan (3). After a brief, initial respite, the virus has spread at a rapid pace in India, resulting in more than 10 million confirmed cases as of December, 2020 with more than 145,000 deaths (4).

Patients diagnosed with COVID-19 have primarily respiratory symptoms. Most patients diagnosed with COVID-19 experience mild to moderate respiratory illness, fever, dry cough, fatigue and recover without requiring special treatment (5). Oxygen desaturation is the hallmark of progression. Patients with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. These patients may develop viral pneumonia, with resultant dyspnea and hypoxemia which may progress to respiratory or multi- system failure and even death (6). There is paucity of large-scale data of the clinical characteristics, outcomes of COVID-19 in the Indian population and evaluation of risk factors with an unfavorable outcome at a national level. Identification of such potential risk factors is important to anticipate medical treatment and to reduce the mortality burden for severe COVID-19 illness by proactive interventions.

The Indian Council of Medical Research (ICMR) conducted a randomized trial (A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease, PLACID TRIAL) to determine the effectiveness and safety of convalescent plasma in patients with moderate COVID-19 to limit progression to severe disease (7). Patients enrolled received standard of care for COVID-19 in keeping with the institutional protocols, based on the best available evidence at the time and guidelines for the management of COVID-19 issued by national health authorities. Participants in the

intervention arm received two doses of 200 mL of convalescent plasma, transfused 24 hours apart, in addition to standard of care. The control arm did not receive any additional therapy. The study concluded that the use of convalescent plasma was not associated with a reduction in 28-day mortality (7).

The aim of this analysis was to identify risk factors associated with mortality by mining the data collected from the cohort enrolled in the PLACID TRIAL (7).

Methods

Participants

The study enrolled patients from 39 different hospitals, of which, 29 were teaching public hospitals and 10 were private facilities spread across 14 states and union territories. Patients over the age of 18 years who were confirmed to have COVID-19 based on a positive SARS-CoV-2 RT-PCR test and moderately ill with either a partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200-300 or respiratory rate >24/min and decreased oxygen saturation on room air (SpO_2 < 93%) were included. Patients were followed up for 28 days and assessed for their health status and all-cause mortality. Ethics approval was obtained from the ICMR Central Ethics Committee on Human Research (CECHR-002/2020) as well as from the Institutional Review Boards (IRB) /Institutional Ethics Committees of all the participating hospitals. Written consent was obtained from patients or their families before enrolling in the study.

Data

Data were obtained from the ICMR PLACID TRIAL database collected in structured paper case record forms and entered in Research Electronic Data Capture system (REDCap, version 8·5 Vanderbilt University, TN). The trial protocol was registered with the Clinical Trial Registry of India (CTRI/2020/04/024775). After the trial was completed, based on cooperative agreement between the centers, and IRB permission, the data was shared and analyzed further, to explore for other meaningful results. No separate ethical clearance was taken for this study.

Demographic, clinical, laboratory tests and outcome data were collected prospectively. Clinical symptoms need for organ support (respiratory, hemodynamic), laboratory tests (complete blood count, coagulation profile, serum biochemical profile, renal and liver function tests) were monitored serially on day of enrollment (day 0) and on day 1, 3, 5, 7, 14 and 28. Inflammatory biomarkers

[lactate dehydrogenase (LDH), serum ferritin, and C-reactive protein (CRP)] and were tested at admission and on day 3 and 7 whereas, Interleukin 6 (IL-6) was done at admission and on day 3.

The outcome of interest was all-cause day 28 mortality. We evaluated for association between laboratory parameters and mortality.

Statistical Methods:

Mean and standard deviation (SD) or median and inter-quartile range (IQR) were used for continuous variables as appropriate, and categorical variables number and proportions were used. To find the association between mortality and study variables, Chi-square test/Fisher's exact test were used. To find the mean difference across the groups, independent t test was used. Similarly, Mann Whitney U test was used to compare median difference. Clinically important baseline variables and time dependent covariates were included in multivariable Cox proportional hazards model. Two multivariate models were developed. The first model included clinical and laboratory parameters tested on day 0, 1, 3, 5, 7, 14 and 28 while the second included inflammatory biomarkers tested on day 0, 3 and 7 after adjusting for age and comorbidities. Variables included parameters that were strongly associated with mortality at univariable analysis or known from previous literature to be strongly associated with outcome. The model assumption was verified using log-log S (t) plots and Global test. A p-value of less than 0·05 levels was considered as statistically significant. All statistical analyses were performed using STATA version 16·0 (StataCorp. 2019. College Station, TX).

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. The study results will be disseminated to the study participants via their treating doctors.

Results:

The PLACID Trial recruited 464 eligible patients for the study. The primary outcome at 28 days was not available for two patients who were lost to follow-up after discharge; nine patients withdrew consent after randomization and two patients did not receive the intervention after randomization as a matched donor was not available. The cohort with known outcome at 28 days thus comprised of 451 patients (*supplementary*).

PLACID TRIAL Mortality Assessment

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the analysis did not adjust for convalescent plasma intervention. The distribution of patients in intervention and control arms were 50·3% (n=227) and 49·7% (n=224), respectively. The mean (SD) age of the cohort was 51 ± 12·4 years; 76·7% were male. Table 1 shows distribution of demographic variables and clinical parameters in the study population.

The most common presenting symptoms were shortness of breath (91·6%), fatigue (78·7%), cough (68·5%) and fever (35%). Comorbidities were present in 59·9% of patients; 28·2% had two or more comorbidities. The most frequent comorbidities were diabetes (43·5%), hypertension (37·5%), obesity (6·9%) and Chronic Obstructive Pulmonary Disease (COPD) (3·3%). There was history of smoking in 8·2%. The time from onset of symptoms to admission was four days (IQR 3-7 days). Majority of the patients required non-invasive (98·9%) ventilatory support. The median duration of respiratory support was six days (IQR 4-10 days). In this cohort, 4% patients required vasopressor support. None of the patients required Extra Corporeal Membrane Oxygenation (ECMO) or dialysis support.

The all-cause mortality at 28 days was 14·4% (95%CI: 11·5-17·9, n=65). Median time from symptom onset to hospital admission was four days in survivors (IQR 3-7 days) and non survivors (IQR 3-6 days). The frequency of shortness of breath, cough and fatigue were similar in survivors and non survivors; however, the presence of fever at admission was significantly (p=0·04) associated with death (table 1). Other than COPD and CKD (chronic kidney disease), other comorbidities were not significantly associated with death (table 1). Admission SOFA score was higher in non survivors. The need for invasive mechanical ventilation, duration of invasive mechanical ventilation and vasopressor therapy were associated with death (table 1).

On univariable analysis (table 2), there was an association between increasing age and mortality. Patients with two or more comorbidities had a 2·25 (1·17-4·32, p=0·014) times increased chance of mortality. There was a strong mortality association for admission platelet count < 100 * 10^9/L (HR 6·53, 95%CI: 3·10-13·75, p <0 ·001), neutrophil lymphocyte ratio (NLR) > 10 (27·49, 11·67-64·75, p <0·001), LDH ≥ 450 IU/L (4·88, 2·73-8·72, p <0·001), D-dimer >1mg/L (3·35, 1·55-7·23, p=0·002) and ferritin >500ng/ml (4·09, 2·31-7·23, p <0·001). Admission IL-6 levels were significantly (p <0.001) higher (76.00, 18.27-171.77) in non survivors than in survivors (18.51, 4.26-56.86). By day 3, IL-6 levels dropped to 11.6 (2.64-45.84) in survivors while it nearly doubled in non-survivors

(140.35, 21.56-427.36). Univariate analysis of CRP did not show any statistical significance (1.0003, 0.99-1.001, p=0.150).

The need for invasive ventilation and vasopressors were associated with death (table 2). Increasing SOFA score was associated with mortality (1·61, 1·48-1·75, p <0·001). The mean SOFA score at day 0 was 2·30 and 3·05 for survivors and non-survivors respectively. The difference in the SOFA score progressively increased between the two groups over time (figure 1). Mortality proportionately also increased with lower PaO_2/FiO_2 values with hazard ratio of 23·11 (12·81-41·69, p <0·001) in severe group as compared to mild group.

Two models were run for multivariable Cox proportional hazards regression analysis over a period of time. Model A included age, comorbidities, PaO_2/FiO_2, NLR and SOFA score. Model A revealed significant hazard ratios for PaO_2/FiO_2 ratio < 100 (3·37, 1·54-7·41, p=0·002), NLR > 10 (9·38, 3·67-23·99, p <0·001), SOFA score (1·21, 1·07- 1·36, p=0·002) after adjusting for age and comorbidities. Model B included age, comorbidities, D-dimer, ferritin and LDH. D-dimer >1 mg/L (2·51, 1·14-5·51, p=0·022), ferritin >500 ng/ml (2·66, 1·46-4·85, p=0·001) and LDH ≥ 450 IU/L (2·96, 1·61-5·45, p=0·001), were associated with mortality after adjusting for age and comorbidities (table 2). IL-6 was omitted from the model as it was not measured on Day 7. CRP was not included in the model as it did not show significant difference between the two groups.

Discussion:

In this study that enrolled patients from across India, we were able to identify clinical, biomarkers (D-dimer, LDH, ferritin) and SOFA score as factors that could indicate increased risk of death in moderately ill COVID-19 patients from PLACID trial cohort. The definition of clinical grading of severity is different in India as compared to other countries (8–12). Mortality of patients critically ill with COVID-19 varies significantly among the published case series, ranging from 16% to 78% (13–19). Similarly two studies from Wuhan which included moderately as well as critically ill patients have shown mortality rate of 3.77% and 14.14% (20,21). This wide variability can be explained by differences in the age of the population, distribution of risk factors, health system response across different countries, varied treatment protocols and follow-up. In a series of critically ill patients in China, 28-day ICU mortality was 61·5% (22). In a multicentric study from Italy, the mortality risk for patient without respiratory failure at admission was of 1% after 15 days while survival in patients with a moderate-to-severe respiratory failure (PaO_2/FiO_2 ≤200 mm Hg) at admission was only 56% at 15 days (23). The fatality rate reported in Europe and the United States of America is significantly

higher than in China (24). Therefore, findings obtained in a specific country might not be automatically extrapolated and national cohorts must be studied.

In our study population, mortality increased with age, which is similar to the pattern observed in other countries affected by COVID-19. Age seems to affect the time from hospitalization to death. Age-specific death rates was quite similar in studies from Asia, Europe and North America (25). South Korea, Italy, France, Germany, England and Wales, and Spain COVID-19 attributed mortality rates rise by about 12%/year while the United States and Wuhan, China showed a slower rate of increase about 9·5%/year of age (26). In a meta-analysis of 61,11,583 subjects, 23·2% of patients were aged ≥80 years and showed an average mortality rate of 12·10%, the lowest being in China (3·1%) and the highest in the United Kingdom (20·8%) and New York State (20·99%). In the same study, highest mortality rate was observed in patients aged ≥80 years. The largest increase in mortality risk was observed in patients aged 60 to 69 years compared with those aged 50 to 59 years (odds ratio 3·13, 95% CI: 2·61-3·76) (27).

Presence of comorbidities significantly increases the death risk of COVID-19. A higher risk of mortality was seen in our patients who had CKD and COPD. Meta-analysis, including 1389 COVID-19 patients with 19·7% having severe disease showed a significant association of CKD with severe COVID-19 with pooled odds ratio as 3·03 (28). Similarly, the estimated mortality risk in patients with COPD was three times of those without (p<0·05) (29). We found that 43·5% of our patients had diabetes which is markedly higher as compared to patients from Korea which showed that 16·97% had diabetes mellitus (30). Our analysis showed that the presence of diabetes was not significantly different between survivors and non survivors (42·5% vs· 49·2%, p=0·310), in contrast to the study from South Korea (30) which showed a much higher mortality among diabetic patients than in those without (20·0% vs· 4·8%). Hypertension and obesity were not significantly different among survivors and non-survivors in our study. However, the presence of two or more comorbidities was associated with mortality in our study.

Univariable Cox proportional hazards regression modeling identified several other prognostic markers for mortality, most notably age ≥60 years, PaO_2/FiO_2 ratio <100, NLR >10, platelet count <100 x 10^9/L, ferritin >500ng/ml, LDH >450 IU/L and D-dimer >1mg/L. Our study showed similar findings when compared with studies from Wuhan (31). Older age, leukocytosis, and high LDH level have been reported to be risk factors associated with in-hospital death in other studies also (32–34).

IL-6 levels were significantly different in survivors and non-survivors at admission. By day 3 survivors had reducing IL-6 while it nearly doubled in non survivors.

Mortality was higher among patients requiring invasive mechanical ventilation (HR 19·57, 11.81-32.41, p=<0.001) and those requiring vasopressors (HR 11·36, 6.47-19.96, p=<0.001). However, the median duration of invasive ventilation for survivors was 12 days (2, 14) and that for non-survivors was one day (1,3). These results suggest that patients with acute respiratory failure from COVID-19 may recover, even with severe disease requiring longer ventilation, and that probably the sickest patients die early reflecting lower duration of invasive ventilation in non survivors. Therefore, invasive ventilation should be timely and effectively provided.

In our study, the SOFA score was recognized as a valuable tool that could be used to prognosticate outcome of patients with COVID-19. Univariate and multivariate regression analysis both showed that the increase in SOFA score was related to mortality, with a clearly divergent pattern between the two groups. Thus, an increasing SOFA score over time may be a factor that can be used to identify a subset of patients who may have an unfavorable outcome. Studies have shown that the SOFA score could be used to evaluate severity and 60-day mortality of COVID-19 with the optimal cut-off score of 5 (35).

Limitations of the study includes the variability of treatment provided in the multiple centres. The participants of this study may not comprise a true observational cohort as this was a post hoc analysis of a randomized control trial data and extrapolation to the general population must be carefully qualified.

The risk factors identified in this study include older age with two or more comorbidities, mainly history of COPD and CKD. Multivariate analysis showed lymphopenia, lower PaO2/ FiO2 ratio, increased LDH, ferritin and D-dimer were significantly associated with mortality. A rising IL-6 may portent a poor prognosis. Serial SOFA score can be used for prognostication. Understanding the symptoms, burden of comorbidities, systematic monitoring key laboratory parameters offer new methods of improving reducing mortality in COVID-19.

FOOTNOTES:

Authors Contributions:

Study design: JJM, LJ, JVP

Clinical Management: SK, LT, AZ, JER, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG.

Data collection: JJM, SK, LT, AZ, AA, AM, GK, PC, TB, JER, PR, MM, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG, PDY, GS, HK, VSK.

Data Analysis: JJM, SK, LJ, TM, MJ, PR, MM, DD, JVP.

Data Interpretation: JJM, SK, AZ, LJ, JER, TM, MJ, DD, JVP

Manuscript writing: JJM, SK, LT, AZ, LJ, JER, BC, TM, MJ, PR, MM, DD, JVP, AA, AM, GK, HK, PC, TB

Study Administration: JJM, BC, JVP, AA, AM, GK, HK, PC, TB

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org. LJ was member of the independent Data and Safety Monitoring Board for the PLACID trial. He did not receive any remuneration for the primary study. This is a secondary study conducted using data collected from patients enrolled during the PLACID trial. No new patient was enrolled during this study.

Ethical Approval: Ethical approval was obtained from the ICMR Central Ethics Committee on Human Research (CECHR-002/2020) based in the National Center for Disease Informatics and Research, Indian Council of Medical Research, Bengaluru, Karnataka, as well as from the Institutional Review Boards (IRB) /Institutional Ethics Committees of all the participating hospitals.

Data availability statement: Data will be made available, upon request, and must be accompanied by a brief proposal outlining the analysis plan. A signed data access agreement might be needed to ensure data safety and compliance with national rules about data sharing.

Acknowledgement: We acknowledge ICMR for providing us the data collected during PLACID trial which was analyzed in the present study.

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Table 1: Distribution of demographic variables and clinical parameters in enrolled patients and comparison of survivors and non-survivors in the cohort

Variables		Overall (n=451) N (%)	Survivor (n=386) N (%)	Non survivor (n=65) N (%)	P value
Age (Mean ± SD)		51±12·4	50±12·4	56±11·3	**<0·001***
Age	**≤ 40**	104 (23·1)	97 (25·1)	7 (10·8)	**0·004**
	41-59	225 (49·9)	194 (50·3)	31 (47·7)	
	≥60	122 (27·0)	95 (24·6)	27 (41·5)	
Gender: Male		346 (76·7)	294(76·2)	52 (80·0)	0·499
Blood group	**A**	104(23·1)	91(23·6)	13(20·0)	0·530
	B	164(36·4)	140(36·3)	24(36·9)	
	AB	25(5·5)	19(4·9)	6(9·2)	
	O	158(35·0)	136(35·2)	22(33·9)	
History of smoking		37(8·2)	32(8·3)	5(7·7)	0·866
Comorbidities					
Diabetes		196 (43·5)	164 (42·5)	32 (49·2)	0·310
Hypertension		169 (37·5)	139 (36·0)	30 (46·2)	0·118
Chronic obstructive pulmonary disease		15 (3·3)	10 (2·6)	5 (7·7)	**0·050**
Obesity ≥ 30		31 (6·9)	25 (6·5)	6 (9·2)	0·426
Chronic kidney disease		17 (3·8)	11 (2·9)	6 (9·2)	**0·024**
Coronary artery disease		31 (6·9)	23 (6·0)	8 (12·3)	0·106
Cerebrovascular disease		4 (0·9)	3 (0·8)	1 (1·5)	0·465
Symptoms at admission					
Shortness of breath		413 (91·6)	351 (90·9)	62 (95·4)	0·232
Fever		158 (35·0)	128 (33·2)	30 (46·2)	**0·042**
Cough		309 (68·5)	259 (67·1)	50 (76·9)	0·115
Fatigue		354 (78·7)	301 (78·2)	53 (81·5)	0·541
Severity of illness score					
SOFA score at admission*		2·40 ± 1·06	2·30±0·93	3·05±1·49	**<0·001**
Treatment					
Vasopressor		18 (4·0)	1 (0·3)	17 (26·6)	**<0·001**
Non-Invasive Ventilation (NIV)		446 (98·9)	383 (99·2)	63 (96·9)	0·101
Invasive ventilation		38 (8·4)	4 (1·04)	34 (52·31)	**<0·001**
Interval between symptoms onset to admission ǂ		4 (3, 7)	4 (3, 7)	4 (3, 6)	0·996
Duration of respiratory support days ǂ		6 (4, 10)	6 (4, 9·5)	6 (3, 10)	0·688
Duration of invasive ventilation days ǂ		1 (1,3)	12 (2, 14)	1 (1, 3)	**0·019**
Duration of hospital stay days ǂ		14 (10, 18)	14 (11, 19)	8 (5, 14)	**<0·001**

ǂ Median (IQR) days in days – Mann Whitney U test was used

*Mean ± SD – Independent t test was used

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Table 2: Univariate and Multivariable Cox-regression for baseline characteristics, Laboratory parameters and Inflammatory biomarkers

Variables		Univariate Cox regression			Multivariable Cox regression (Model A)			Multivariable Cox regression (Model B)		
		HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	≤40	1·00			1·00			1·00		
	41-59	2·04	0·90 – 4·65	0·089	1·25	0·51 – 3·09	0·623	1·55	0·66 – 3·63	0·310
	≥60	3·51	1·53 – 8·06	**0·003**	1·42	0·57 – 3·54	0·456	1·72	0·71 – 4·19	0·231
Gender	Male	1·19	0·65 – 2·18	0·581						
Blood Group	O	1·00								
	A	0·94	0·47 – 1·88	0·868						
	B	1·13	0·63 – 2·02	0·693						
	AB	2·01	0·81 – 4·97	0·132						
Comorbidities	No Comorbidities	1·00			1·00			1·00		
	1	1·62	0·81 – 3·24	0·172	1·22	0·60 – 2·49	0·586	1·31	0·60 – 2·85	0·503
	2 or More	2·25	1·17 – 4·32	**0·014**	1·78	0·90 – 3·51	0·095	2·66	1·29 – 5·51	**0·008**
Neutrophil/Lymphocyte ratio ǂ	<5	1·00			1·00					
	5-10	4·88	1·82 – 13·06	**0·002**	3·24	1·19 – 8·80	**0·021**			
	>10	27·49	11·67 – 64·75	**<0·001**	9·38	3·67 – 23·99	**<0·001**			
Platelet count ǂ **(* 10^9/L)**	<100	6·53	3·10 – 13·75	**<0·001**						
	≥ 100	1·00								
SOFA score ǂ		1·61	1·48 – 1·75	**<0·001**	1·21	1·07 – 1·36	**0·002**			
D-dimer(mg/L) $	<0·5	1·00						1·00		
	0·5 - 1·0	1·53	0·63 – 3·68	0·347				1·29	0·53 – 3·14	0·568
	>1·0	3·35	1·55 – 7·23	**0·002**				2·51	1·14 – 5·51	**0·022**
Ferritin(ng/mL) $	<500	1·00						1·00		
	≥500	4·09	2·31 – 7·23	**<0·001**				2·66	1·46 – 4·85	**0·001**
CRP$ (mg/L)		1·0003	0·999 – 1·001	**0·150**						
LDH$ (IU/L)	<450	1·00						1·00		
	≥ 450	4·88	2·73 – 8·72	**<0·001**				2·96	1·61 – 5·45	**0·001**
PaO2/FiO2ǂ	<100 (severe)	23·11	12·81 – 41·69	**<0·001**	3·37	1·54 – 7·41	**0·002**			
	100-200(moderate)	5·63	2·97 – 10·68	**<0·001**	1·84	0·88 – 3·82	0·103			
	>200 (Mild)	1·00			1·00					
Interval from onset of symptoms to admission		1·05	0·97 – 1·12	0·228						
Vasopressor support		11·36	6·47 – 19·96	**<0·001**						
Invasive ventilation support		19·57	11·81 – 32·41	**<0·001**						

ǂ Laboratory Parameters were measured at day 0,1,3,5,7 and day 14: $ Inflammatory biomarkers values were measured at day 0,3 and day 7
(Model A) Multivariable Cox model for Age, comorbidities with Laboratory Parameters, **(Model B)** Multivariable Cox model for Age, comorbidities with inflammatory biomarker values

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Figure 1:

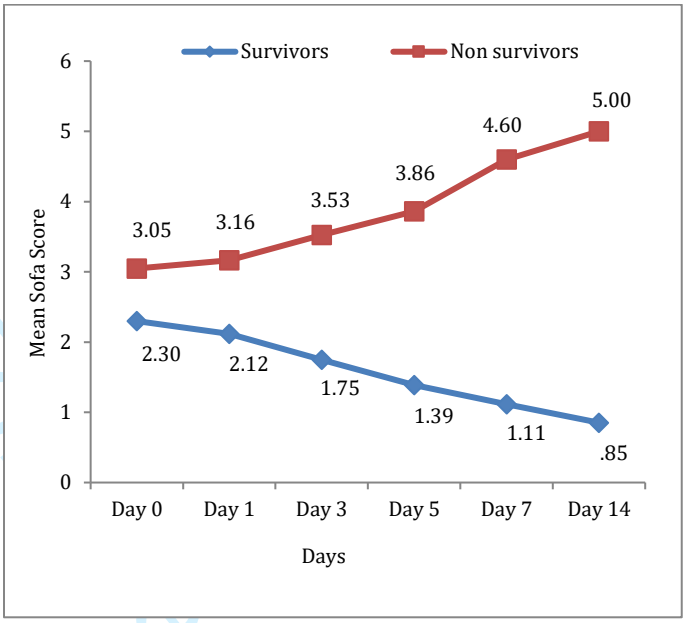

Figure 1: Line graph for SOFA score showing difference between survivors and non survivors

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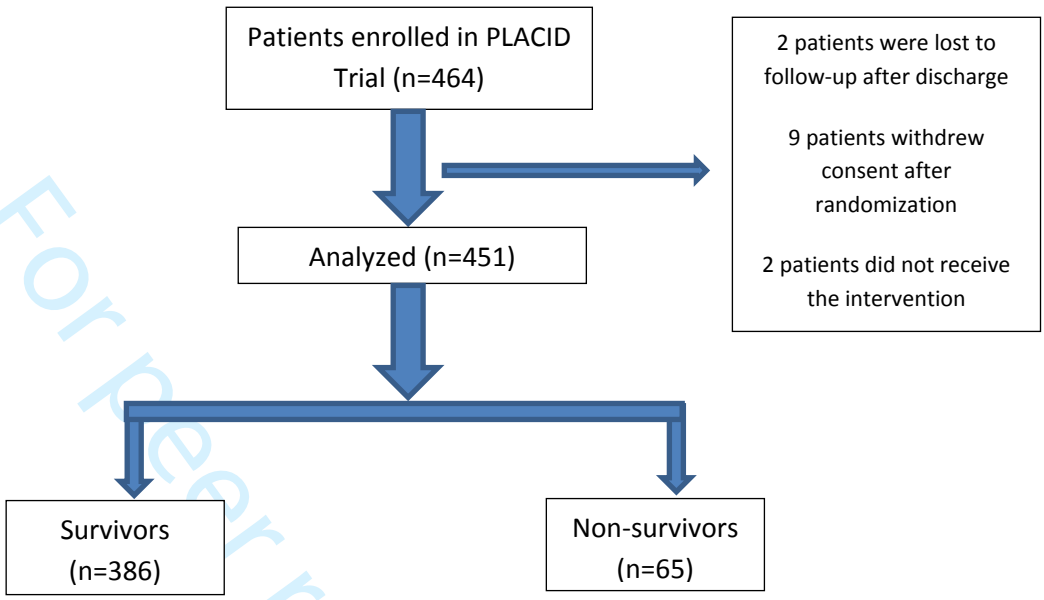
Supplementary

Flowchart for the study protocol



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Factors associated with mortality among moderate and severe COVID 19 patients – secondary analysis of a Randomized Controlled Trial

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PLACID TRIAL Mortality Assessment

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Abstract

Objective:

Large data on the clinical characteristics and outcome of COVID-19 in the Indian population is scarce. We analyzed the factors associated with mortality in a cohort of moderate to severely ill COVID-19 patients enrolled in a randomized trial on convalescent plasma.

Setting:

39 public and private hospitals across India.

Participants:

Of the 464 patients recruited, two were lost to follow-up, nine withdrew consent and two patients did not receive the intervention after randomization. The cohort of 451 participants with known outcome at 28-days was analyzed.

Design:

Secondary analysis of data from a Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease (PLACID TRIAL).

Primary outcome measure:

Factors associated with all-cause mortality at 28-days post-enrolment.

Results:

The mean (SD) age was 51±12·4 years; 76·7% were males. Admission SOFA score was 2·4±1·1. Non-invasive ventilation, invasive ventilation and vasopressor therapy were required in 98·9%, 8·4% and 4·0% respectively. The 28-day mortality was 14·4%. Median time from symptom onset to hospital admission was similar in survivors (4 days; IQR 3-7) and non survivors (4 days; IQR 3-6). Patients with two or more co-morbidities had 2·25 (95%CI: 1·18–4·29, p=0·014) times risk of death. When compared with survivors, admission IL-6 levels were higher (p<0.001) in non-survivors and increased further on Day 3. On multivariable Fine and Gray model , severity of illness (SHR 1·22, 95%CI:1·11-1·35,p<0.001), PaO_2/FiO_2 ratio <100 (3·47, 1·64-7·37, p=0·001), Neutrophil Lymphocyte ratio (NLR) >10 (9·97, 3·65-27.13, p<0·001), D-dimer >1·0mg/L (2·50,1·14-5·48, p=0·022), ferritin ≥500ng/mL (2·67, 1·44-4·96, p=0·002) and LDH ≥450 IU/L (2·96, 1·60-5·45, p=0·001) were significantly associated with death.

Conclusion:

In this cohort of moderate to severely ill COVID-19 patients, severity of illness, underlying co-morbidities and higher levels of inflammatory markers were significantly associated with death.

Trial Registration:

The trial protocol was registered with the Clinical Trial Registry of India (CTRI/2020/04/024775).

Article Summary

Strengths and limitations of this study

Strengths

There is no study from India, with representation from multiple states that has detailed the clinical profile and evaluated for factors associated with death. This study may help with strategic planning at a national level.

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the present analysis need not be adjusted for convalescent plasma intervention.

There may be variability of treatment provided in the multiple centres, however, care was taken that patients received best standard of care for COVID-19 dictated by the best available evidence at the time and guidelines for the management of COVID-19 issued by health authorities of the Indian government.

Limitations

The laboratory and biomarker assays for ferritin, lactate dehydrogenase, C reactive protein, and D-dimer were conducted using tests from different manufacturers.

Participants of this study may not comprise a true observational cohort as this was a post hoc analysis of a randomized control trial data, also our study did not analyse the effect of SARS-CoV-2 variants causing a high mortality in younger population during the second wave of COVID-19 infection, therefore extrapolation to the general population must be carefully qualified.

Introduction

The first human case of Corona Virus Disease 19 (COVID-19) caused by the novel coronavirus (named Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2) was reported in Wuhan City, China in December 2019. On 30 January 2020, the World Health Organization (WHO) declared that the outbreak of COVID-19 constituted a Public Health Emergency of International Concern (1). Based on the high levels of global spread and the severity of COVID-19, on 11 March 2020, the Director-General of the WHO declared the COVID-19 outbreak a pandemic (2). The sudden outbreak followed by rapid spread in a globalized world, resulted in a major medical burden, besides affecting socio-economic well-being among all nations.

In India, the disease was first detected on 30 January 2020 in the state of Kerala, in a student who returned from Wuhan (3). After a brief, initial respite, the virus has spread at a rapid pace in India, resulting in more than 10 million confirmed cases as of December, 2020 with more than 145,000 deaths (4).

Patients diagnosed with COVID-19 have primarily respiratory symptoms. Most patients diagnosed with COVID-19 experience mild to moderate respiratory illness, fever, dry cough, fatigue and recover without requiring special treatment (5). Oxygen desaturation is the hallmark of progression. Patients with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. These patients may develop viral pneumonia, with resultant dyspnea and hypoxemia which may progress to respiratory or multi- system failure and even death (6). There is paucity of large-scale data on the clinical characteristics, outcomes of COVID-19 in the Indian population and evaluation of risk factors with an unfavorable outcome at a national level. Identification of such potential risk factors is important to anticipate medical treatment and to reduce the mortality burden for severe COVID-19 illness by proactive interventions.

The Indian Council of Medical Research (ICMR) conducted a randomized trial (A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease, PLACID TRIAL) to determine the effectiveness and safety of convalescent plasma in patients with moderate to severely ill COVID-19 to limit progression of disease (7). Patients received standard of care for COVID-19 in keeping with the institutional protocols, based on the best available evidence at the time and guidelines for the management of COVID-19 issued by national health authorities. Participants in the intervention

arm received two doses of 200 mL of convalescent plasma, transfused 24 hours apart, in addition to standard of care. The control arm did not receive any additional therapy. The study concluded that the use of convalescent plasma was not associated with a reduction in 28-day mortality (7).

The aim of this analysis was to identify risk factors associated with mortality by mining the data collected from the cohort enrolled in the PLACID TRIAL (7).

Methods

Participants

The study enrolled patients from 39 different hospitals, of which, 29 were teaching public hospitals and 10 were private facilities spread across 14 states and union territories. Patients over the age of 18 years who were confirmed to have COVID-19 based on a positive SARS-CoV-2 RT-PCR test and moderate to severely ill with either a partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200-300 or respiratory rate >24/min and decreased oxygen saturation on room air (SpO_2 < 93%) were included during the study period from 22 April to 14 July 2020. Patients were followed up for 28-days and assessed for their health status and all-cause mortality. Ethics approval was obtained from the ICMR Central Ethics Committee on Human Research (CECHR-002/2020) as well as from the Institutional Review Boards (IRB) /Institutional Ethics Committees of all the participating hospitals. Written consent was obtained from patients or their families before enrolling in the study.

Data

Data was obtained from the ICMR PLACID TRIAL database collected in structured paper case record forms and entered in Research Electronic Data Capture system (REDCap, version 8·5 Vanderbilt University, TN). The trial protocol was registered with the Clinical Trial Registry of India (CTRI/2020/04/024775). After trial completion, based on cooperative agreement between the centers, and IRB permission, the data was shared and analyzed further, to explore for other meaningful results. No separate ethical clearance was taken for this study.

Demographic, clinical, laboratory tests and outcome data were collected prospectively. Clinical symptoms need for organ support (respiratory, hemodynamic), laboratory tests (complete blood count, coagulation profile, serum biochemical profile, renal and liver function tests) were monitored serially on day of enrollment (day 0) and on day 1, 3, 5, 7, 14 and 28. Inflammatory

biomarkers [lactate dehydrogenase (LDH), serum ferritin, and C-reactive protein (CRP)] were tested at admission and on day 3 and 7 whereas; Interleukin 6 (IL-6) was done at admission and on day 3.

The outcome of interest was all-cause day 28 mortality. We evaluated for association between laboratory parameters and mortality.

Statistical Methods:

Mean and standard deviation (SD) or median and inter-quartile range (IQR) were used for continuous variables as appropriate, and categorical variables number and proportions were used. To find the association between mortality and study variables, Chi-square test/Fisher's exact test were used. To find the mean difference across the groups, independent t test was used. Similarly, Mann Whitney U test was used to compare median difference. The end point of interest was all-cause mortality (event of interest) at day 28 from the time of enrollment, discharged alive (competing event) and hospital admission after day 28 (censored), whichever is earlier. Discharged alive was treated as a competing event because the event of discharged alive precludes the event of all-cause mortality. Clinically important baseline variables and time dependent covariates were included in multivariable Fine and Gray regression model for competing endpoints and sub-distribution hazard ratios were presented. Two multivariable models were developed. The first model included clinical and laboratory parameters tested on day 0, 1, 3, 5, 7, 14 and 28 while the second included inflammatory biomarkers tested on day 0, 3 and 7 after adjusting for age and comorbidities. For certain laboratory markers such as D-dimer, ferritin and LDH, clinically relevant thresholds were used for the analysis rather than using these data as continuous variables. The clinically relevant thresholds for these variables were set as >1.0 mg/L for D-dimer, ≥500 mg/mL for Ferritin and ≥450 IU/L for LDH. Variables included parameters that were strongly associated with mortality at univariate analysis or known from previous literature to be strongly associated with outcome. The model assumption was verified using log-log S (t) plots and Global test. A p-value of less than 0·05 levels was considered as statistically significant. All statistical analyses were performed using STATA version 16·0 (StataCorp. 2019. College Station, TX).

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. The study results will be disseminated to the study participants via their treating doctors.

Results

The PLACID Trial recruited 464 eligible patients for the study. The primary outcome at 28-days was not available for two patients who were lost to follow-up after discharge; nine patients withdrew consent after randomization and two patients did not receive the intervention after randomization as a matched donor was not available. The cohort with known outcome at 28 days thus comprised of 451 patients (*supplementary*).

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the analysis did not adjust for convalescent plasma intervention. The distribution of patients in intervention and control arms were 50·3% (n=227) and 49·7% (n=224), respectively. The mean (SD) age of the cohort was 51 ± 12·4 years; 76·7% were males. Table 1 shows distribution of demographic variables and clinical parameters in the study population.

The most common presenting symptoms were shortness of breath (91·6%), fatigue (78·7%), cough (68·5%) and fever (35%). Comorbidities were present in 59.9% of patients; 31.7% had any one comorbidities and 28·2% had two or more comorbidities. The most frequent comorbidities were diabetes (43·5%), hypertension (37·5%), obesity (6·9%) and Chronic Obstructive Pulmonary Disease (COPD) (3·3%). There was history of smoking in 8·2%. The time from onset of symptoms to admission was four days (IQR 3-7 days). Majority of the patients required non-invasive (98·9%) ventilatory support. The median duration of respiratory support was six days (IQR 4-10 days). In this cohort, 4% patients required vasopressor support. None of the patients required Extra Corporeal Membrane Oxygenation (ECMO) or dialysis support.

The all-cause mortality at 28-days was 14·4% (95%CI: 11·5-17·9, n=65). Median time from symptom onset to hospital admission was four days in survivors (IQR 3-7 days) and non survivors (IQR 3-6 days). The frequency of shortness of breath, cough and fatigue were similar in survivors and non survivors; however, the presence of fever at admission was significantly (p=0·042) associated with death (table 1). Other than COPD and CKD (chronic kidney disease), other

comorbidities were not significantly associated with death (table 1). Admission Sequential Organ Failure Assessment (SOFA) score was higher in non survivors. The need for invasive mechanical ventilation, duration of invasive mechanical ventilation and vasopressor therapy were associated with death (table 1).

On univariate analysis (table 2), there was an association between increasing age and mortality. Patients with two or more comorbidities had a 2·25 (95%CI: 1·18-4·29, p=0·014) times increased chance of mortality. There was a strong mortality association for platelet count <100 * 10^9/L (SHR 6·88, 95%CI: 3·61-13·13, p<0·001), neutrophil lymphocyte ratio (NLR) >10 (28.84, 11·92-69.76, p<0·001), LDH ≥450 IU/L (4·88, 2·72-8·75, p<0·001), D-dimer >1mg/L (3·34, 1·55-7·19, p=0·002) and ferritin ≥500ng/mL (4·11, 2·28-7·41, p<0·001). Admission IL-6 levels were significantly (p<0.001) higher (76.00, 18.27-171.77) in non survivors than in survivors (18.51, 4.26-56.86). By day 3, IL-6 levels dropped to 11.6 (2.64-45.84) in survivors while it nearly doubled in non-survivors (140.35, 21.56-427.36). Univariate analysis of CRP did not show any statistical significance (1.0003, 0.999-1.001, p=0.080).

The need for invasive ventilation and vasopressors were associated with death (table 2). Increasing SOFA score was associated with mortality (1·63, 1·54-1·74, p<0·001). The mean SOFA score at day 0 was 2·30 and 3·05 for survivors and non-survivors respectively. The difference in the SOFA score progressively increased between the two groups over time (figure 1). Mortality proportionately also increased with lower PaO_2/FiO_2 values with sub-distribution hazard ratio of 25.64 (14.8-44.41, p<0·001) in the severe group as compared to the mild group.

Two models were run for multivariable Fine and Gray regression model over a period of time (table 3). Model A included age, comorbidities, PaO_2/FiO_2, NLR and SOFA score. Model A revealed significant sub-distribution hazard ratios for PaO_2/FiO_2 ratio <100 (3·47, 1·64-7·37, p=0·001), NLR >10 (9·97, 3·65-27.13, p<0·001), SOFA score (1·22, 1·11- 1·35, p<0·001) after adjusting for age and comorbidities. Model B included age, comorbidities, D-dimer, ferritin and LDH. D-dimer >1 mg/L (2·50, 1·14-5·48, p=0·022), ferritin ≥500 ng/mL (2·67, 1·44-4·96, p=0·002) and LDH ≥450 IU/L (2·96, 1·60-5·45, p=0·001), were associated with mortality after adjusting for age and comorbidities (table 3). IL-6 was omitted from the model as it was not measured on Day 7.

Discussion

In this study that enrolled patients from across India, we were able to identify clinical, biomarkers (D-dimer, LDH, ferritin) and SOFA score as factors that could indicate increased risk of death in moderately to severely ill COVID-19 patients from PLACID trial cohort. The definition of clinical grading of severity is different in India as compared to other countries (8–12). Mortality of critically ill COVID-19 patients varies significantly among the published case series, ranging from 16% to 78% (13–19). Similarly two studies from Wuhan, which included moderately as well as critically ill patients, have shown mortality rates of 3.77% and 14.14% (20,21). This wide variability can be explained by differences in the age of the population, distribution of risk factors, health system response across different countries, varied treatment protocols and follow-up. In a series of critically ill patients in China, 28-day ICU mortality was 61·5% (22). In a multicentric study from Italy, the mortality risk for patients without respiratory failure at admission was of 1% after 15 days while survival in patients with moderate-to-severe respiratory failure (PaO_2/FiO_2 ≤200 mm Hg) at admission was only 56% at 15 days (23). The fatality rate reported in Europe and the United States of America is significantly higher than in China (24). Therefore, findings obtained in a specific country might not be automatically extrapolated and national cohorts must be studied.

In our study population, mortality increased with age, which is similar to the pattern observed in other countries affected by COVID-19. Age seems to affect the time from hospitalization to death. Age-specific death rates was quite similar in studies from Asia, Europe and North America (25). South Korea, Italy, France, Germany, England and Wales, and Spain COVID-19 attributed mortality rates rise by about 12%/year while the United States and Wuhan, China showed a slower rate of increase about 9·5%/year of age (26). In a meta-analysis of 61, 11,583 subjects, 23·2% of patients were aged ≥80 years and showed an average mortality rate of 12·10%, the lowest being in China (3·1%) and the highest in the United Kingdom (20·8%) and New York State (20·99%). In the same study, highest mortality rate was observed in patients aged ≥80 years. The largest increase in mortality risk was observed in patients aged 60 to 69 years compared with those aged 50 to 59 years (odds ratio 3·13, 95% CI: 2·61-3·76) (27).

Presence of comorbidities significantly increases the death risk of COVID-19. A higher risk of mortality was seen in our patients who had CKD and COPD. Meta-analysis, including 1389 COVID-19 patients with 19·7% having severe disease showed a significant association of CKD with severe COVID-19 with pooled odds ratio as 3·03 (28). Similarly, the estimated mortality risk in patients

with COPD was three times of those without (p<0·05) (29). We found that 43·5% of our patients had diabetes which is markedly higher as compared to patients from Korea which showed that 16·97% had diabetes mellitus (30). Our analysis showed that the presence of diabetes was not significantly different between survivors and non survivors (42·5% vs. 49·2%, p=0·310), in contrast to the study from South Korea (30) which showed a much higher mortality among diabetic patients than in those without (20·0% vs. 4·8%). Hypertension and obesity were not significantly different among survivors and non-survivors in our study. However, the presence of two or more comorbidities was associated with mortality in our study.

Univariate Fine-Gray model identified several other prognostic markers for mortality, most notably age ≥60 years, PaO_2/FiO_2 ratio <100, NLR >10, platelet count <100 x 10^9/L, ferritin >500ng/mL, LDH >450 IU/L and D-dimer >1mg/L. Our study showed similar findings when compared with studies from Wuhan (31). Older age, leukocytosis, and high LDH level have been reported to be risk factors associated with in-hospital death in other studies also (32–34). IL-6 levels were significantly different in survivors and non-survivors at admission. By day 3 survivors had reducing IL-6 while it nearly doubled in non survivors.

Mortality was higher among patients requiring invasive mechanical ventilation (SHR 19·57, 12.21-31.35, p<0.001) and those requiring vasopressors (SHR 11·36, 7.79-16.56, p<0.001). However, the median duration of invasive ventilation for survivors was 12 days (2, 14) and that for non-survivors was one day (1, 3). These results suggest that patients with acute respiratory failure from COVID-19 may recover, even with severe disease requiring longer ventilation, and that probably the sickest patients die early reflecting lower duration of invasive ventilation in non survivors. Therefore, invasive ventilation should be timely and effectively provided.

In our study, the SOFA score was recognized as a valuable tool that could be used to prognosticate outcome of patients with COVID-19. Univariate and multivariable competing risk regression models showed that the increase in SOFA score was related to mortality, with a clearly divergent pattern between the two groups. Thus, an increasing SOFA score over time may be a factor that can be used to identify a subset of patients who may have an unfavorable outcome. Studies have shown that the SOFA score could be used to evaluate severity and 60-day mortality of COVID-19 with the optimal cut-off score of 5 (35).

Limitations of the study include the variability of treatment provided in the multiple centers. The participants of this study may not comprise a true observational cohort as this was a post hoc analysis of a randomized control trial data and extrapolation to the general population must be carefully qualified. Our study did not analyse the effect of SARS-CoV-2 variants causing a high mortality in younger population during the second wave of COVID-19 infection and this may limit generalizability of the data to the second wave. Despite these limitations, this study provides a comprehensive overview of prognostic factors in moderate to severely ill COVID-19 patients that included patients from across the country.

Conclusion

A favorable outcome can be expected in moderate to severely ill COVID-19 patients. Older age, multiple comorbidities, low PaO2/FiO2 ratio and deranged inflammatory markers are associated with worse prognosis. Serial SOFA score can be used for prognostication. Understanding symptoms, burden of comorbidities and systematic monitoring of key laboratory parameters offer opportunities for targeted intervention in COVID-19 with the use of anti-inflammatory or immunomodulatory agents.

Figure legend

Figure 1 showing serial Sequential Organ Failure Assessment (SOFA) score among survivors and non-survivors. Increasing SOFA score was associated with mortality. The mean SOFA score at day 0 was 2•30 and 3•05 for survivors and non-survivors respectively. The difference in the SOFA score showed divergence between the two groups over time.

FOOTNOTES:

Authors Contributions:

Study design: JJM, LJ, JVP

Clinical Management: SK, LT, AZ, JER, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG.

Data collection: JJM, SK, LT, AZ, AA, AM, GK, PC, TB, JER, PR, MM, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG, PDY, GS, HK, VSK.

Data Analysis: JJM, SK, LJ, TM, MJ, PR, MM, DD, JVP.

Data Interpretation: JJM, SK, AZ, LJ, JER, TM, MJ, DD, JVP

Manuscript writing: JJM, SK, LT, AZ, LJ, JER, BC, TM, MJ, PR, MM, DD, JVP, AA, AM, GK, HK, PC, TB

Study Administration: JJM, BC, JVP, AA, AM, GK, HK, PC, TB

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Competing interests: 'None declared'. All authors have completed the ICMJE uniform disclosure form at www.icmje.org.

Ethical Approval: Ethical approval was obtained from the ICMR Central Ethics Committee on Human Research (CECHR-002/2020) based in the National Center for Disease Informatics and Research, Indian Council of Medical Research, Bengaluru, Karnataka, as well as from the Institutional Review Boards (IRB) /Institutional Ethics Committees of all the participating hospitals.

Data availability statement: Data will be made available, upon request, and must be accompanied by a brief proposal outlining the analysis plan. A signed data access agreement might be needed to ensure data safety and compliance with national rules about data sharing.

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PLACID TRIAL Mortality Assessment

Table 1: Distribution of demographic variables and clinical parameters in enrolled patients and comparison of survivors and non-survivors in the cohort

Variables		Overall (n=451) N (%)	Survivor (n=386) N (%)	Non survivor (n=65) N (%)	P value
Age (Mean ± SD)		51±12·4	50±12·4	56±11·3	**<0·001***
Age	**≤ 40**	104 (23·1)	97 (25·1)	7 (10·8)	**0·004**
	41-59	225 (49·9)	194 (50·3)	31 (47·7)	
	≥60	122 (27·1)	95 (24·6)	27 (41·5)	
Gender: Male		346 (76·7)	294(76·2)	52 (80·0)	0·499
Blood group	**A**	104(23·1)	91(23·6)	13(20·0)	0·518
	B	164(36·4)	140(36·3)	24(36·9)	
	AB	25(5·5)	19(4·9)	6(9·2)	
	O	158(35·0)	136(35·2)	22(33·8)	
History of smoking		37(8·2)	32(8·3)	5(7·7)	0·866
Comorbidities and Chronic illness					
Diabetes		196 (43·5)	164 (42·5)	32 (49·2)	0·310
Hypertension		169 (37·5)	139 (36·0)	30 (46·2)	0·118
Chronic obstructive pulmonary disease		15 (3·3)	10 (2·6)	5 (7·7)	**0·050**
Obesity ≥ 30		31 (6·9)	25 (6·5)	6 (9·2)	0·426
Chronic kidney disease		17 (3·8)	11 (2·8)	6 (9·2)	**0·024**
Coronary artery disease		31 (6·9)	23 (6·0)	8 (12·3)	0·106
Cerebrovascular disease		4 (0·9)	3 (0·8)	1 (1·5)	0·465
Symptoms at admission					
Shortness of breath		413 (91·6)	351 (90·9)	62 (95·4)	0·232
Fever		158 (35·0)	128 (33·2)	30 (46·2)	**0·042**
Cough		309 (68·5)	259 (67·1)	50 (76·9)	0·115
Fatigue		354 (78·7)	301 (78·2)	53 (81·5)	0·541
Severity of illness score					
SOFA score at admission*		2·40 ± 1·06	2·30±0·93	3·05±1·49	**<0·001**
Treatment					
Vasopressor		18 (4·0)	1 (0·3)	17 (26·6)	**<0·001**
Non-Invasive Ventilation (NIV)		446 (98·9)	383 (99·2)	63 (96·9)	0·101
Invasive ventilation		38 (8·4)	4 (1·04)	34 (52·31)	**<0·001**
Interval between symptoms onset to admission ǂ		4 (3, 7)	4 (3, 7)	4 (3, 6)	0·996
Duration of respiratory support days ǂ		6 (4, 10)	6 (4, 9·5)	6 (3, 10)	0·689
Duration of invasive ventilation days ǂ		1 (1,3)	12 (2, 14)	1 (1, 3)	**0·020**
Duration of hospital stay days ǂ		14 (10, 18)	14 (11, 19)	8 (5, 14)	**<0·001**

ǂ Median (IQR) days in days – Mann Whitney U test was used

***Mean ± SD – Independent t test was used**

PLACID TRIAL Mortality Assessment

Table 2: Univariate Fine and Gray model for baseline characteristics, laboratory parameters and inflammatory biomarkers

Variables		Univariate Analysis					
		Mortality			Discharged alive		
		SHR	95% CI	P value	SHR	95% CI	P value
Age	≤40	1·00			1·00		
	41-59	2.04	0.90 - 4.66	0.089	0.80	0.64 – 1.01	**0.057**
	≥60	3.51	1.53 - 8.07	**0.003**	0.56	0.42 - 0.73	**<0.001**
Gender	Male	1.19	0.64 - 2.19	0.582	0.87	0.70 - 1.09	0.228
Blood Group	O	1·00			1·00		
	A	0.94	0.48 - 1.87	0.866	0.89	0.69 - 1.15	0.389
	B	1.13	0.63 - 2.01	0.689	0.93	0.75 - 1.18	0.578
	AB	2.01	0.80 - 5.05	0.139	0.66	0.39 - 1.11	0.116
Comorbidities	No Comorbidities	1·00			1·00		
	1	1.62	0.82 - 3.21	0.166	0.79	0.63 - 0.99	**0.044**
	2 or More	2.25	1.18 - 4.29	**0.014**	0.70	0.55 - 0.88	**0.003**
Neutrophil/Lymphocyte ratio ǂ	<5	1·00			1·00		
	5-10	4.90	1.80 - 13.32	**0.002**	0.72	0.56 - 0.93	**0.013**
	>10	28.84	11.92 - 69.76	**<0.001**	0.17	0.12 - 0.26	**<0.001**
Platelet count ǂ **(* 10^9/L)**	<100	6.88	3.61 – 13.13	**<0.001**	0.16	0.05 - 0.49	**0.001**
	≥ 100	1·00			1·00		
SOFA score ǂ		1.63	1.54 - 1.74	**<0.001**	0.62	0.57 - 0.67	**<0.001**
D-dimer(mg/L) $	<0·5	1·00			1·00		
	0·5 - 1·0	1.53	0.63 - 3.67	0.346	0.82	0.64 - 1.06	0.129
	>1·0	3.34	1.55 - 7.19	**0.002**	0.57	0.45 - 0.73	**<0.001**
Ferritin(ng/mL) $	<500	1·00			1·00		
	≥500	4.11	2.28 - 7.41	**<0.001**	0.52	0.42 - 0.64	**<0.001**
CRP$ (mg/L)		1.0003	0.999 - 1.001	0.080	0.99	0.99 - 1.00	0.360
LDH$ (IU/L)	<450	1·00			1·00		
	≥ 450	4.88	2.72 - 8.75	**<0.001**	0.53	0.43 - 0.66	**<0.001**
PaO2/FiO2ǂ	<100 (severe)	25.64	14.8 - 44.41	**<0.001**	6.5e-08	4.3e-08 - 9.9e-08	**<0.001**
	100-200(moderate)	5.97	3.05 - 11.69	**<0.001**	0.19	0.10 - 0.36	**<0.001**
	>200 (Mild)	1·00			1·00		
Interval from onset of symptoms to admission		1.05	0.96 - 1.14	0.334	0.97	0.94 - 1.00	0.058
Vasopressor support		11.36	7.79 - 16.56	**<0.001**	0.03	0.004 - 0.22	**0.001**
Invasive ventilation support		19.57	12.21 - 31.35	**<0.001**	0.01	0.002 - 0.09	**<0.001**

ǂ Laboratory Parameters were measured at day 0, 1,3,5,7 and day 14: $ inflammatory biomarkers values were measured at day 0, 3 and day 7.SHR: Sub-distribution Hazard ratio; CI: Confidence Interval

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Table 3: Multivariable Fine and Gray Model for baseline characteristics, laboratory parameters and inflammatory biomarkers

Variables		Multivariable Analysis (Model A)						Multivariable Analysis (Model B)					
		Mortality			Discharged alive			Mortality			Discharged alive		
		SHR	95% CI	P value	SHR	95% CI	P value	SHR	95% CI	P value	SHR	95% CI	P value
Age	≤40	1·00			1·00			1·00			1·00		
	41-59	1.23	0.60 - 2.49	0.572	1.03	0.81 - 1.32	0.825	1.55	0.65 - 3.71	0.325	0.95	0.74 - 1.21	0.671
	≥60	1.44	0.67 - 3.09	0.347	0.94	0.70 - 1.26	0.675	1.72	0.67 - 4.46	0.261	0.78	0.57 - 1.06	0.110
Comorbidities	No Comorbidities	1·00			1·00			1·00			1·00		
	1	1.20	0.69 - 2.10	0.515	0.91	0.72 - 1.14	0.407	1.31	0.59 - 2.91	0.509	0.87	0.67 - 1.11	0.254
	2 or More	1.76	1.02 - 3.03	**0.041**	0.89	0.69 - 1.14	0.329	2.68	1.26 - 5.70	**0.011**	0.69	0.52 - 0.93	**0.014**
Neutrophil/Lymphocyte ratio ǂ	<5	1·00			1·00								
	5-10	3.34	1.21 - 9.19	**0.020**	0.81	0.64 - 1.03	0.095						
	>10	9.97	3.65 - 27.13	**<0.001**	0.39	0.26 - 0.58	**<0.001**						
SOFA score ǂ		1.22	1.11 - 1.35	**<0.001**	0.75	0.68 - 0.83	**<0.001**						
D-dimer(mg/L) $	<0·5							1.00					
	0·5 - 1·0							1.29	0.54 - 3.10	0.565	0.84	0.65 - 1.09	0.198
	>1·0							2.50	1.14 - 5.48	**0.022**	0.64	0.49 - 0.82	**<0.001**
Ferritin(ng/mL) $	<500							1·00			1·00		
	≥500							2.67	1.44 - 4.96	**0.002**	0.69	0.55 - 0.86	**0.001**
LDH$ (IU/L)	<450							1·00			1·00		
	≥ 450							2.96	1.60 - 5.45	**0.001**	0.68	0.55 - 0.85	**0.001**
PaO2/FiO2ǂ	<100 (severe)	3.47	1.64 - 7.37	**0.001**	3.1e-07	1.7e-07 - 5.7e-07	**<0.001**						
	100-200(moderate)	1.91	0.91 - 4.004	0.087	0.401	0.19 - 0.85	**0.016**						
	>200 (Mild)	1·00			1·00								

ǂ Laboratory Parameters were measured at day 0, 1,3,5,7 and day 14: $ Inflammatory biomarkers values were measured at day 0, 3 and day 7

(Model A) Multivariable Fine and Gray model for Age, comorbidities with Laboratory Parameters, (Model B) Multivariable Fine and Gray model for Age, comorbidities with inflammatory biomarker values

SHR: Sub-distribution Hazard ratio; CI: Confidence Interval

PLACID TRIAL Mortality Assessment

Figure 1:

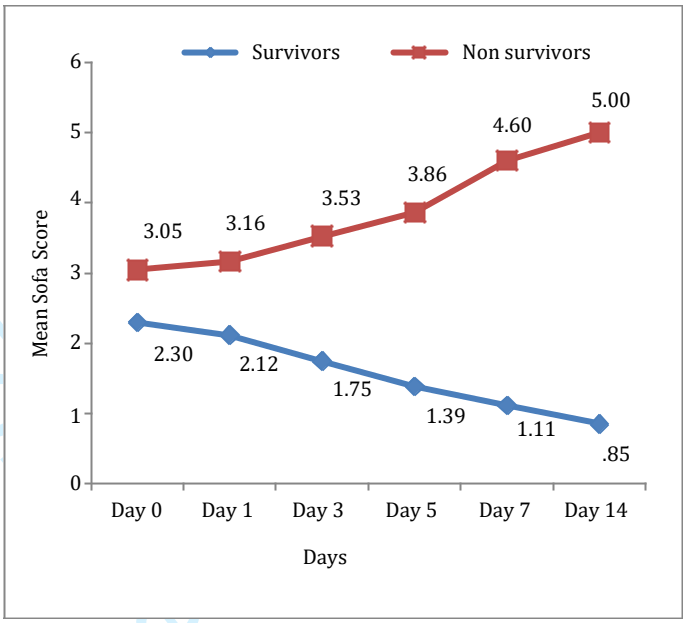

Figure 1: Line graph for SOFA score showing difference between survivors and non survivors

Figure 1 showing serial Sequential Organ Failure Assessment (SOFA) score among survivors and non-survivors. Increasing SOFA score was associated with mortality. The mean SOFA score at day 0 was 2•30 and 3•05 for survivors and non-survivors respectively. The difference in the SOFA score showed divergence between the two groups over time.

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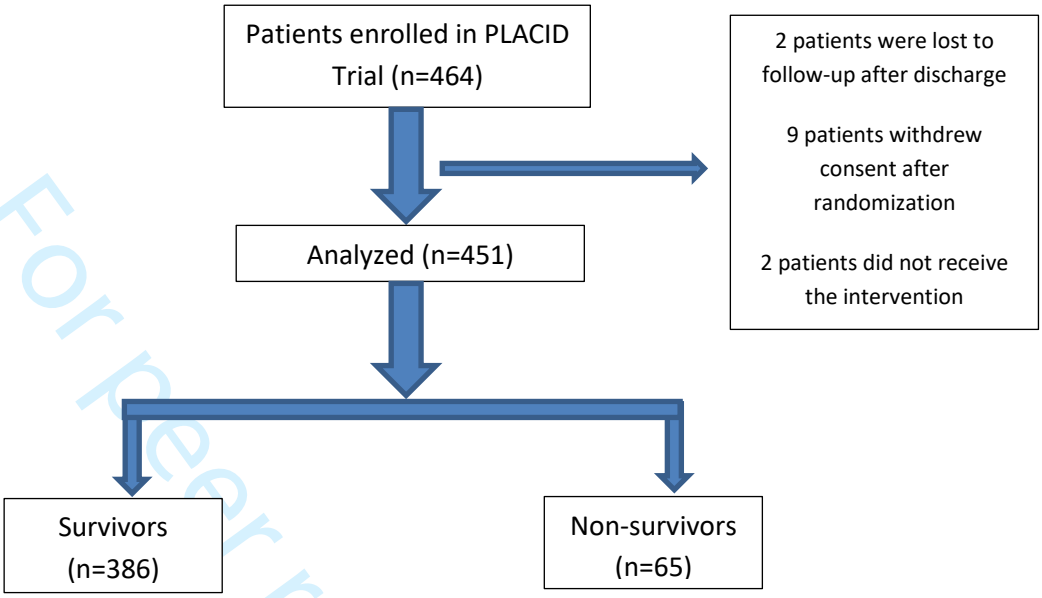
Supplementary

Flowchart for the study protocol



The Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease (PLACID) Trial recruited 464 eligible patients for the study. The primary outcome at 28 days was not available for two patients who were lost to follow-up after discharge; nine patients withdrew consent after randomization and two patients did not receive the intervention after randomization as a matched donor was not available. The cohort with known outcome at 28 days thus comprised of 451 patients out of whom 386 survived and 65 died.

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Primary Subject	Public health

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PLACID TRIAL Mortality Assessment

Factors associated with mortality among moderate and severe COVID 19 patients in India – A secondary analysis of a Randomised Controlled Trial

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PLACID TRIAL Mortality Assessment

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Abstract

Objective:

Large data on the clinical characteristics and outcome of COVID-19 in the Indian population is scarce. We analysed the factors associated with mortality in a cohort of moderate and severely ill COVID-19 patients enrolled in a randomised trial on convalescent plasma.

Design:

Secondary analysis of data from a Phase II, Open Label, Randomised Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease (PLACID TRIAL).

Setting:

39 public and private hospitals across India, during the study period 22 April 2020 to 14 July 2020.

Participants:

Of the 464 patients recruited, two were lost to follow-up, nine withdrew consent and two patients did not receive the intervention after randomisation. The cohort of 451 participants with known outcome at 28-days was analysed.

Primary outcome measure:

Factors associated with all-cause mortality at 28-days post-enrolment.

Results:

The mean (SD) age was 51±12·4 years; 76·7% were males. Admission SOFA score was 2·4±1·1. Non-invasive ventilation, invasive ventilation and vasopressor therapy were required in 98·9%, 8·4% and 4·0% respectively. The 28-day mortality was 14·4%. Median time from symptom onset to hospital admission was similar in survivors (4 days; IQR 3-7) and non survivors (4 days; IQR 3-6). Patients with two or more co-morbidities had 2·25 (95%CI: 1·18–4·29, p=0·014) times risk of death. When compared with survivors, admission IL-6 levels were higher (p<0.001) in non-survivors and increased further on Day 3. On multivariable Fine and Gray model , severity of illness (SHR 1·22, 95%CI:1·11-1·35,p<0.001), PaO_2/FiO_2 ratio <100 (3·47, 1·64-7·37, p=0·001), Neutrophil Lymphocyte ratio (NLR) >10 (9·97, 3·65-27.13, p<0·001), D-dimer >1·0mg/L (2·50,1·14-5·48, p=0·022), ferritin ≥500ng/mL (2·67, 1·44-4·96, p=0·002) and LDH ≥450 IU/L (2·96, 1·60-5·45, p=0·001) were significantly associated with death.

Conclusion:

In this cohort of moderate and severely ill COVID-19 patients, severity of illness, underlying co-morbidities and higher levels of inflammatory markers were significantly associated with death.

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Trial Registration:

CTRI/2020/04/024775.

Article Summary

Strengths and limitations of this study

Strengths

There is no study from India, with representation from multiple states that has detailed the clinical profile and evaluated for factors associated with death. This study may help with strategic planning at a national level.

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the present analysis need not be adjusted for convalescent plasma intervention.

There may be variability of treatment provided in the multiple centres, however, care was taken that patients received best standard of care for COVID-19 dictated by the best available evidence at the time and guidelines for the management of COVID-19 issued by health authorities of the Indian government.

Limitations

The laboratory and biomarker assays for ferritin, lactate dehydrogenase, C reactive protein, and D-dimer were conducted using tests from different manufacturers.

Participants of this study may not comprise a true observational cohort as this was a post hoc analysis of a randomised control trial data. Our study did not analyse the effect of SARS-CoV-2 variants causing a high mortality in younger population during the second wave of COVID-19 infection, and therefore extrapolation to the general population must be carefully qualified.

Introduction

The first human case of Corona Virus Disease 19 (COVID-19) caused by the novel coronavirus (named Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2) was reported in Wuhan City, China in December 2019. On 30 January 2020, the World Health Organisation (WHO) declared that the outbreak of COVID-19 constituted a Public Health Emergency of International Concern (1). Based on the high levels of global spread and the severity of COVID-19, on 11 March 2020, the Director-General of the WHO declared the COVID-19 outbreak a pandemic (2). The sudden outbreak followed by rapid spread in a globalised world, resulted in a major medical burden, besides affecting socio-economic well-being among all nations.

In India, the disease was first detected on 30 January 2020 in the state of Kerala, in a student who returned from Wuhan (3). After a brief, initial respite, the virus has spread at a rapid pace in India, resulting in more than 10 million confirmed cases as of December, 2020 with more than 145,000 deaths (4).

Patients diagnosed with COVID-19 have primarily respiratory symptoms. Most patients diagnosed with COVID-19 experience mild to moderate respiratory illness, fever, dry cough, fatigue and recover without requiring special treatment (5). Oxygen desaturation is the hallmark of progression. Patients with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. These patients may develop viral pneumonia, with resultant dyspnoea and hypoxaemia which may progress to respiratory or multi- system failure and even death (6). There is paucity of large-scale data on the clinical characteristics, outcomes of COVID-19 in the Indian population and evaluation of risk factors with an unfavourable outcome at a national level. Identification of such potential risk factors is important to anticipate medical treatment and to reduce the mortality burden for severe COVID-19 illness by proactive interventions.

The Indian Council of Medical Research (ICMR) conducted a randomised trial (A Phase II, Open Label, Randomised Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease, PLACID TRIAL) to determine the effectiveness and safety of convalescent plasma in patients with moderate and severely ill COVID-19 to limit progression of disease (7). Patients received standard of care for COVID-19 in keeping with the institutional protocols, based on the best available evidence at the time and guidelines for the management of COVID-19 issued by national health authorities. Participants in the intervention

arm received two doses of 200 mL of convalescent plasma, transfused 24 hours apart, in addition to standard of care. The control arm did not receive any additional therapy. The study concluded that the use of convalescent plasma was not associated with a reduction in 28-day mortality (7).

The aim of this analysis was to identify risk factors associated with mortality by mining the data collected from the cohort enrolled in the PLACID TRIAL (7).

Methods

Participants

The study enrolled patients from 39 different hospitals, of which, 29 were teaching public hospitals and 10 were private facilities spread across 14 states and union territories. Patients over the age of 18 years who were confirmed to have COVID-19 based on a positive SARS-CoV-2 RT-PCR test and moderate and severely ill with either a partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200-300 or respiratory rate >24/min and decreased oxygen saturation on room air (SpO_2 < 93%) were included during the study period from 22 April to 14 July 2020. As per the guidelines issued by the Ministry of Health, Government of India at the time of conduct of the study, the subset of patients with the above criteria but with a respiratory rate between 24 and 30/min were classified as moderate disease. Those with respiratory rate >30 breaths/min were classified as severe disease(8). Patients were followed up for 28-days and assessed for their health status and all-cause mortality. Ethics approval was obtained from the ICMR Central Ethics Committee on Human Research (CECHR-002/2020) as well as from the Institutional Review Boards (IRB) /Institutional Ethics Committees of all the participating hospitals. Written consent was obtained from patients or their families before enrolling in the study.

Data

Data was obtained from the ICMR PLACID TRIAL database collected in structured paper case record forms and entered in Research Electronic Data Capture system (REDCap, version 8·5 Vanderbilt University, TN). The trial protocol was registered with the Clinical Trial Registry of India (CTRI/2020/04/024775). After trial completion, based on co-operative agreement between the centres, and IRB permission, the data was shared and analysed further, to explore for other meaningful results. No separate ethical clearance was taken for this study.

PLACID TRIAL Mortality Assessment

Demographic, clinical, laboratory tests and outcome data were collected prospectively. Clinical symptoms need for organ support (respiratory, haemodynamic), laboratory tests (complete blood count, coagulation profile, serum biochemical profile, renal and liver function tests) were monitored serially on day of enrolment (day 0) and on day 1, 3, 5, 7, 14 and 28. Inflammatory biomarkers [lactate dehydrogenase (LDH), serum ferritin, and C-reactive protein (CRP)] were tested at admission and on day 3 and 7 whereas; Interleukin 6 (IL-6) was done at admission and on day 3.

The outcome of interest was all-cause day 28 mortality. We evaluated for association between laboratory parameters and mortality.

Statistical Methods:

Mean and standard deviation (SD) or median and inter-quartile range (IQR) were used for continuous variables as appropriate, and categorical variables number and proportions were used. To find the association between mortality and study variables, Chi-square test/Fisher's exact test were used. To find the mean difference across the groups, independent t test was used. Similarly, Mann Whitney U test was used to compare median difference. The end point of interest was all-cause mortality (event of interest) at day 28 from the time of enrolment, discharged alive (competing event) and hospital admission after day 28 (censored), whichever is earlier. Discharged alive was treated as a competing event because the event of discharged alive precludes the event of all-cause mortality. The variables that are statistically significant or clinically important are considered in the multivariable Fine and Gray regression model . However, if a variable is expected to have collinear concern or had sparse data that was not included in the analysis. Two multivariable models were developed. The first model included clinical and laboratory parameters tested on day 0, 1, 3, 5, 7, 14 and 28 while the second included inflammatory biomarkers tested on day 0, 3 and 7 after adjusting for age and comorbidities. For certain laboratory markers such as D-dimer, ferritin and LDH, clinically relevant thresholds were used for the analysis rather than using these data as continuous variables. The clinically relevant thresholds for these variables were set as >1.0 mg/L for D-dimer, ≥500 mg/mL for Ferritin and ≥450 IU/L for LDH. The threshold for Ferritin of 500 µg/L was based on the cut-off value for the diagnosis of Hemophagocytic lymphohistiocytosis (HLH) as well as some preliminary evidence in COVID that a threshold of >500 µg/L was associated with invasive ventilator dependence(9). Similarly, traditionally a threshold of <0.5 mg/L is used to exclude pulmonary thromboembolism; in this context two thresholds were used, 0.5 to 1.0 mg/L

and >1.0 mg/L(10). Variables included parameters that were strongly associated with mortality at univariate analysis or known from previous literature to be strongly associated with outcome. The model assumption was verified using log-log S (t) plots and Global test. A p-value of less than 0·05 levels was considered as statistically significant. All statistical analysis were performed using STATA version 16·0 (StataCorp. 2019. College Station, TX).

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. The study results will be disseminated to the study participants via their treating doctors.

Results

The PLACID Trial recruited 464 eligible patients for the study. The primary outcome at 28-days was not available for two patients who were lost to follow-up after discharge; nine patients withdrew consent after randomisation and two patients did not receive the intervention after randomisation as a matched donor was not available. The cohort with known outcome at 28 days thus comprised of 451 patients (*supplementary*).

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the analysis did not adjust for convalescent plasma intervention. The distribution of patients in intervention and control arms were 50·3% (n=227) and 49·7% (n=224), respectively. The mean (SD) age of the cohort was 51 ± 12·4 years; 76·7% were males. Table 1 shows distribution of demographic variables and clinical parameters in the study population.

The most common presenting symptoms were shortness of breath (91·6%), fatigue (78·7%), cough (68·5%) and fever (35%). Comorbidities were present in 59.9% of patients; 31.7% had any one comorbidities and 28·2% had two or more comorbidities. The most frequent comorbidities were diabetes (43·5%), hypertension (37·5%), obesity (6·9%) and Chronic Obstructive Pulmonary Disease (COPD) (3·3%). There was history of smoking in 8·2%. The time from onset of symptoms to admission was four days (IQR 3-7 days). Majority of the patients required non-invasive (98·9%) ventilatory support. The median duration of respiratory support was six days (IQR 4-10 days). In this cohort, 4% patients required vasopressor support. None of the patients required Extra Corporeal Membrane Oxygenation (ECMO) or dialysis support.

PLACID TRIAL Mortality Assessment

The all-cause mortality at 28-days was 14·4% (95%CI: 11·5-17·9, n=65). Median time from symptom onset to hospital admission was four days in survivors (IQR 3-7 days) and non survivors (IQR 3-6 days). The frequency of shortness of breath, cough and fatigue were similar in survivors and non survivors; however, the presence of fever at admission was significantly (p=0·042) associated with death (table 1). Other than COPD and CKD (chronic kidney disease), other comorbidities were not significantly associated with death (table 1). Admission Sequential Organ Failure Assessment (SOFA) score was higher in non survivors. The need for invasive mechanical ventilation, duration of invasive mechanical ventilation and vasopressor therapy were associated with death (table 1).

On univariate analysis (table 2), there was an association between increasing age and mortality. Patients with two or more comorbidities had a 2·25 (95%CI: 1·18-4·29, p=0·014) times increased chance of mortality. There was a strong mortality association for platelet count <100 * 10^9/L (SHR 6·88, 95%CI: 3·61-13·13, p<0·001), neutrophil lymphocyte ratio (NLR) >10 (28.84, 11·92-69.76, p<0·001), LDH ≥450 IU/L (4·88, 2·72-8·75, p<0·001), D-dimer >1mg/L (3·34, 1·55-7·19, p=0·002) and ferritin ≥500ng/mL (4·11, 2·28-7·41, p<0·001). Admission IL-6 levels were significantly (p<0.001) higher (76.00, 18.27-171.77) in non survivors than in survivors (18.51, 4.26-56.86). By day 3, IL-6 levels dropped to 11.6 (2.64-45.84) in survivors while it nearly doubled in non-survivors (140.35, 21.56-427.36). CRP did not show any statistical significance (1.0003, 0.999-1.001, p=0.080).

The need for invasive ventilation and vasopressors were associated with death (table 2). Increasing SOFA score was associated with mortality (1·63, 1·54-1·74, p<0·001). The mean SOFA score at day 0 was 2·30 and 3·05 for survivors and non-survivors respectively. The difference in the SOFA score progressively increased between the two groups over time (figure 1). Mortality proportionately also increased with lower PaO_2/FiO_2 values with sub-distribution hazard ratio of 25.64 (14.8-44.41, p<0·001) in the severe group as compared to the mild group.

Two models were run for multivariable Fine and Gray regression model over a period of time (table 3). Model A included age, comorbidities, PaO_2/FiO_2, NLR and SOFA score. Model A revealed significant sub-distribution hazard ratios for PaO_2/FiO_2 ratio <100 (3·47, 1·64-7·37, p=0·001), NLR >10 (9·97, 3·65-27.13, p<0·001), SOFA score (1·22, 1·11- 1·35, p<0·001) after adjusting for age and comorbidities. Model B included age, comorbidities, D-dimer, ferritin and LDH. D-dimer >1 mg/L (2·50, 1·14-5·48, p=0·022), ferritin ≥500 ng/mL (2·67, 1·44-4·96, p=0·002) and LDH ≥450 IU/L

(2·96, 1·60-5·45, p=0·001), were associated with mortality after adjusting for age and comorbidities (table 3). IL-6 was omitted from the model as it was not measured on Day 7.

Discussion

In this study that enrolled patients from across India, we were able to identify clinical, biomarkers (D-dimer, LDH, ferritin) and SOFA score as factors that could indicate increased risk of death in moderate and severely ill COVID-19 patients from PLACID trial cohort. The definition of clinical grading of severity is different in India as compared to other countries (11–15). Mortality of critically ill COVID-19 patients varies significantly among the published case series, ranging from 16% to 78% (16–22). Similarly two studies from Wuhan, which included moderately as well as critically ill patients, have shown mortality rates of 3.77% and 14.14% (23,24). This wide variability can be explained by differences in the age of the population, distribution of risk factors, health system response across different countries, varied treatment protocols and follow-up. In a series of critically ill patients in China, 28-day ICU mortality was 61·5% (25). In a multicentric study from Italy, the mortality risk for patients without respiratory failure at admission was of 1% after 15 days while survival in patients with moderate-to-severe respiratory failure (PaO_2/FiO_2 ≤200 mm Hg) at admission was only 56% at 15 days (26). The fatality rate reported in Europe and the United States of America is significantly higher than in China (27). Therefore, findings obtained in a specific country might not be automatically extrapolated and national cohorts must be studied.

In our study population, mortality increased with age, which is similar to the pattern observed in other countries affected by COVID-19. Age seems to affect the time from hospitalisation to death. Age-specific death rates was quite similar in studies from Asia, Europe and North America (28). South Korea, Italy, France, Germany, England and Wales, and Spain COVID-19 attributed mortality rates rise by about 12%/year while the United States and Wuhan, China showed a slower rate of increase about 9·5%/year of age (29). In a meta-analysis of 61, 11,583 subjects, 23·2% of patients were aged ≥80 years and showed an average mortality rate of 12·10%, the lowest being in China (3·1%) and the highest in the United Kingdom (20·8%) and New York State (20·99%). In the same study, highest mortality rate was observed in patients aged ≥80 years. The largest increase in mortality risk was observed in patients aged 60 to 69 years compared with those aged 50 to 59 years (odds ratio 3·13, 95% CI: 2·61-3·76) (30).

Presence of comorbidities significantly increases the death risk of COVID-19. A higher risk of mortality was seen in our patients who had CKD and COPD. Meta-analysis, including 1389 COVID-

19 patients with 19·7% having severe disease showed a significant association of CKD with severe COVID-19 with pooled odds ratio as 3·03 (31). Similarly, the estimated mortality risk in patients with COPD was three times of those without (p<0·05) (32). We found that 43·5% of our patients had diabetes which is markedly higher as compared to patients from Korea which showed that 16·97% had diabetes mellitus (33). Our analysis showed that the presence of diabetes was not significantly different between survivors and non survivors (42·5% vs. 49·2%, p=0·310), in contrast to the study from South Korea (33) which showed a much higher mortality among diabetic patients than in those without (20·0% vs. 4·8%). Hypertension and obesity were not significantly different among survivors and non-survivors in our study. However, the presence of two or more comorbidities was associated with mortality in our study.

Fine-Gray model identified prognostic markers for mortality, most notably age ≥60 years, PaO_2/FiO_2 ratio <100, NLR >10, platelet count <100 x 10^9/L, ferritin >500ng/mL, LDH >450 IU/L and D-dimer >1mg/L. Our study showed similar findings when compared with studies from Wuhan (34). Older age, leukocytosis, and high LDH level have been reported to be risk factors associated with in-hospital death in other studies also (35–37). IL-6 levels were significantly different in survivors and non-survivors at admission. By day 3 survivors had reducing IL-6 while it nearly doubled in non survivors.

Mortality was higher amongst patients requiring invasive mechanical ventilation (SHR 19·57, 12.21-31.35, p<0.001) and those requiring vasopressors (SHR 11·36, 7.79-16.56, p<0.001). However, the median duration of invasive ventilation for survivors was 12 days (2, 14) and that for non-survivors was one day (1, 3). These results suggest that patients with acute respiratory failure from COVID-19 may recover, even with severe disease requiring longer ventilation, and that probably the sickest patients die early reflecting lower duration of invasive ventilation in non survivors. Therefore, invasive ventilation should be timely and effectively provided.

In our study, the SOFA score was recognised as a valuable tool that could be used to prognosticate outcome of patients with COVID-19. Competing risk regression models showed that the increase in SOFA score was related to mortality, with a clearly divergent pattern between the two groups. Thus, an increasing SOFA score over time may be a factor that can be used to identify a subset of patients who may have an unfavourable outcome. Studies have shown that the SOFA

score could be used to evaluate severity and 60-day mortality of COVID-19 with the optimal cut-off score of 5 (38).

Limitations of the study include the variability of treatment provided in the multiple centres. The participants of this study may not comprise a true observational cohort as this was a post hoc analysis of a randomised control trial data and extrapolation to the general population must be carefully qualified. Our study did not analyse the effect of SARS-CoV-2 variants causing a high mortality in younger population during the second wave of COVID-19 infection and this may limit generalisability of the data to the second wave. Despite these limitations, this study provides a comprehensive overview of prognostic factors in moderate and severely ill COVID-19 patients that included patients from across the country.

Conclusion

Older age, multiple comorbidities, low PaO2/FiO2 ratio and deranged inflammatory markers are associated with worse prognosis. Serial SOFA score can be used for prognostication. Understanding symptoms, burden of comorbidities and systematic monitoring of key laboratory parameters offer opportunities for targeted intervention in COVID-19 with the use of anti-inflammatory or immunomodulatory agents.

Figure legend

Figure 1 showing serial Sequential Organ Failure Assessment (SOFA) score among survivors and non-survivors. Increasing SOFA score was associated with mortality. The mean SOFA score at day 0 was 2•30 and 3•05 for survivors and non-survivors respectively. The difference in the SOFA score showed divergence between the two groups over time.

FOOTNOTES:

Authors Contributions:

Study design: JJM, LJ, JVP

Clinical Management: SK, LT, AZ, JER, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG.

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Data collection: JJM, SK, LT, AZ, AA, AM, GK, PC, TB, JER, PR, MM, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG, PDY, GS, HK, VSK.

Data Analysis: JJM, SK, LJ, TM, MJ, PR, MM, DD, JVP.

Data Interpretation: JJM, SK, AZ, LJ, JER, TM, MJ, DD, JVP

Manuscript writing: JJM, SK, LT, AZ, LJ, JER, BC, TM, MJ, PR, MM, DD, JVP, AA, AM, GK, HK, PC, TB

Study Administration: JJM, BC, JVP, AA, AM, GK, HK, PC, TB

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Competing interests: 'None declared'. All authors have completed the ICMJE uniform disclosure form at www.icmje.org.

Ethical Approval: Ethical approval was obtained from the ICMR Central Ethics Committee on Human Research (CECHR-002/2020) based in the National Center for Disease Informatics and Research, Indian Council of Medical Research, Bengaluru, Karnataka, as well as from the Institutional Review Boards (IRB) /Institutional Ethics Committees of all the participating hospitals.

Data availability statement: Data will be made available, upon request, and must be accompanied by a brief proposal outlining the analysis plan. A signed data access agreement might be needed to ensure data safety and compliance with national rules about data sharing.

Acknowledgement: We acknowledge ICMR for providing us the data collected during PLACID trial which was analysed in the present study.

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Table 1: Distribution of demographic variables and clinical parameters in enrolled patients and comparison of survivors and non-survivors in the cohort

Variables		Overall (n=451) N (%)	Survivor (n=386) N (%)	Non survivor (n=65) N (%)	P value
Age (Mean ± SD)		51±12·4	50±12·4	56±11·3	**<0·001***
Age	**≤ 40**	104 (23·1)	97 (25·1)	7 (10·8)	**0·004**
	41-59	225 (49·9)	194 (50·3)	31 (47·7)	
	≥60	122 (27·1)	95 (24·6)	27 (41·5)	
Gender: Male		346 (76·7)	294(76·2)	52 (80·0)	0·499
Blood group	**A**	104(23·1)	91(23·6)	13(20·0)	0·518
	B	164(36·4)	140(36·3)	24(36·9)	
	AB	25(5·5)	19(4·9)	6(9·2)	
	O	158(35·0)	136(35·2)	22(33·8)	
History of smoking		37(8·2)	32(8·3)	5(7·7)	0·866
Comorbidities and Chronic illness					
Diabetes		196 (43·5)	164 (42·5)	32 (49·2)	0·310
Hypertension		169 (37·5)	139 (36·0)	30 (46·2)	0·118
Chronic obstructive pulmonary disease		15 (3·3)	10 (2·6)	5 (7·7)	**0·050**
Obesity ≥ 30		31 (6·9)	25 (6·5)	6 (9·2)	0·426
Chronic kidney disease		17 (3·8)	11 (2·8)	6 (9·2)	**0·024**
Coronary artery disease		31 (6·9)	23 (6·0)	8 (12·3)	0·106
Cerebrovascular disease		4 (0·9)	3 (0·8)	1 (1·5)	0·465
Symptoms at admission					
Shortness of breath		413 (91·6)	351 (90·9)	62 (95·4)	0·232
Fever		158 (35·0)	128 (33·2)	30 (46·2)	**0·042**
Cough		309 (68·5)	259 (67·1)	50 (76·9)	0·115
Fatigue		354 (78·7)	301 (78·2)	53 (81·5)	0·541
Severity of illness score					
SOFA score at admission*		2·40 ± 1·06	2·30±0·93	3·05±1·49	**<0·001**
Treatment					
Vasopressor		18 (4·0)	1 (0·3)	17 (26·6)	**<0·001**
Non-Invasive Ventilation (NIV)		446 (98·9)	383 (99·2)	63 (96·9)	0·101
Invasive ventilation		38 (8·4)	4 (1·04)	34 (52·31)	**<0·001**
Interval between symptoms onset to admission ǂ		4 (3, 7)	4 (3, 7)	4 (3, 6)	0·996
Duration of respiratory support days ǂ		6 (4, 10)	6 (4, 9·5)	6 (3, 10)	0·689
Duration of invasive ventilation days ǂ		1 (1,3)	12 (2, 14)	1 (1, 3)	**0·020**
Duration of hospital stay days ǂ		14 (10, 18)	14 (11, 19)	8 (5, 14)	**<0·001**

ǂ Median (IQR) days in days – Mann Whitney U test was used

***Mean ± SD – Independent t test was used**

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Table 2: Univariate Fine and Gray model for baseline characteristics, laboratory parameters and inflammatory biomarkers

Variables		Univariate Analysis					
		Mortality			Discharged alive		
		SHR	95% CI	P value	SHR	95% CI	P value
Age	≤40	1·00			1·00		
	41-59	2.04	0.90 - 4.66	0.089	0.80	0.64 – 1.01	**0.057**
	≥60	3.51	1.53 - 8.07	**0.003**	0.56	0.42 - 0.73	**<0.001**
Gender	Male	1.19	0.64 - 2.19	0.582	0.87	0.70 - 1.09	0.228
Blood Group	O	1·00			1·00		
	A	0.94	0.48 - 1.87	0.866	0.89	0.69 - 1.15	0.389
	B	1.13	0.63 - 2.01	0.689	0.93	0.75 - 1.18	0.578
	AB	2.01	0.80 - 5.05	0.139	0.66	0.39 - 1.11	0.116
Comorbidities	No Comorbidities	1·00			1·00		
	1	1.62	0.82 - 3.21	0.166	0.79	0.63 - 0.99	**0.044**
	2 or More	2.25	1.18 - 4.29	**0.014**	0.70	0.55 - 0.88	**0.003**
Neutrophil/Lymphocyte ratio ǂ	<5	1·00			1·00		
	5-10	4.90	1.80 - 13.32	**0.002**	0.72	0.56 - 0.93	**0.013**
	>10	28.84	11.92 - 69.76	**<0.001**	0.17	0.12 - 0.26	**<0.001**
Platelet count ǂ **(* 10^9/L)**	<100	6.88	3.61 – 13.13	**<0.001**	0.16	0.05 - 0.49	**0.001**
	≥ 100	1·00			1·00		
SOFA score ǂ		1.63	1.54 - 1.74	**<0.001**	0.62	0.57 - 0.67	**<0.001**
D-dimer(mg/L) $	<0·5	1·00			1·00		
	0·5 - 1·0	1.53	0.63 - 3.67	0.346	0.82	0.64 - 1.06	0.129
	>1·0	3.34	1.55 - 7.19	**0.002**	0.57	0.45 - 0.73	**<0.001**
Ferritin(ng/mL) $	<500	1·00			1·00		
	≥500	4.11	2.28 - 7.41	**<0.001**	0.52	0.42 - 0.64	**<0.001**
CRP$ (mg/L)		1.0003	0.999 - 1.001	0.080	0.99	0.99 - 1.00	0.360
LDH$ (IU/L)	<450	1·00			1·00		
	≥ 450	4.88	2.72 - 8.75	**<0.001**	0.53	0.43 - 0.66	**<0.001**
PaO2/FiO2ǂ	<100 (severe)	25.64	14.8 - 44.41	**<0.001**	6.5e-08	4.3e-08 - 9.9e-08	**<0.001**
	100-200(moderate)	5.97	3.05 - 11.69	**<0.001**	0.19	0.10 - 0.36	**<0.001**
	>200 (Mild)	1·00			1·00		
Interval from onset of symptoms to admission		1.05	0.96 - 1.14	0.334	0.97	0.94 - 1.00	0.058
Vasopressor support		11.36	7.79 - 16.56	**<0.001**	0.03	0.004 - 0.22	**0.001**
Invasive ventilation support		19.57	12.21 - 31.35	**<0.001**	0.01	0.002 - 0.09	**<0.001**

ǂ Laboratory Parameters were measured at day 0, 1,3,5,7 and day 14: $ inflammatory biomarkers values were measured at day 0, 3 and day 7.SHR: Sub-distribution Hazard ratio; CI: Confidence Interval

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Table 3: Multivariable Fine and Gray Model for baseline characteristics, laboratory parameters and inflammatory biomarkers

Variables		Multivariable Analysis (Model A)						Multivariable Analysis (Model B)					
		Mortality			Discharged alive			Mortality			Discharged alive		
		SHR	95% CI	P value	SHR	95% CI	P value	SHR	95% CI	P value	SHR	95% CI	P value
Age	≤40	1·00			1·00			1·00			1·00		
	41-59	1.23	0.60 - 2.49	0.572	1.03	0.81 - 1.32	0.825	1.55	0.65 - 3.71	0.325	0.95	0.74 - 1.21	0.671
	≥60	1.44	0.67 - 3.09	0.347	0.94	0.70 - 1.26	0.675	1.72	0.67 - 4.46	0.261	0.78	0.57 - 1.06	0.110
Comorbidities	No Comorbidities	1·00			1·00			1·00			1·00		
	1	1.20	0.69 - 2.10	0.515	0.91	0.72 - 1.14	0.407	1.31	0.59 - 2.91	0.509	0.87	0.67 - 1.11	0.254
	2 or More	1.76	1.02 - 3.03	**0.041**	0.89	0.69 - 1.14	0.329	2.68	1.26 - 5.70	**0.011**	0.69	0.52 - 0.93	**0.014**
Neutrophil/Lymphocyte ratio ǂ	<5	1·00			1·00								
	5-10	3.34	1.21 - 9.19	**0.020**	0.81	0.64 - 1.03	0.095						
	>10	9.97	3.65 - 27.13	**<0.001**	0.39	0.26 - 0.58	**<0.001**						
SOFA score ǂ		1.22	1.11 - 1.35	**<0.001**	0.75	0.68 - 0.83	**<0.001**						
D-dimer(mg/L) $	<0·5							1.00					
	0·5 - 1·0							1.29	0.54 - 3.10	0.565	0.84	0.65 - 1.09	0.198
	>1·0							2.50	1.14 - 5.48	**0.022**	0.64	0.49 - 0.82	**<0.001**
Ferritin(ng/mL) $	<500							1·00			1·00		
	≥500							2.67	1.44 - 4.96	**0.002**	0.69	0.55 - 0.86	**0.001**
LDH$ (IU/L)	<450							1·00			1·00		
	≥ 450							2.96	1.60 - 5.45	**0.001**	0.68	0.55 - 0.85	**0.001**
PaO2/FiO2ǂ	<100 (severe)	3.47	1.64 - 7.37	**0.001**	3.1e-07	1.7e-07 - 5.7e-07	**<0.001**						
	100-200(moderate)	1.91	0.91 - 4.004	0.087	0.401	0.19 - 0.85	**0.016**						
	>200 (Mild)	1·00			1·00								

ǂ Laboratory Parameters were measured at day 0, 1,3,5,7 and day 14: $ Inflammatory biomarkers values were measured at day 0, 3 and day 7

(Model A) Multivariable Fine and Gray model for Age, comorbidities with Laboratory Parameters, (Model B) Multivariable Fine and Gray model for Age, comorbidities with inflammatory biomarker values

SHR: Sub-distribution Hazard ratio; CI: Confidence Interval

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Figure 1:

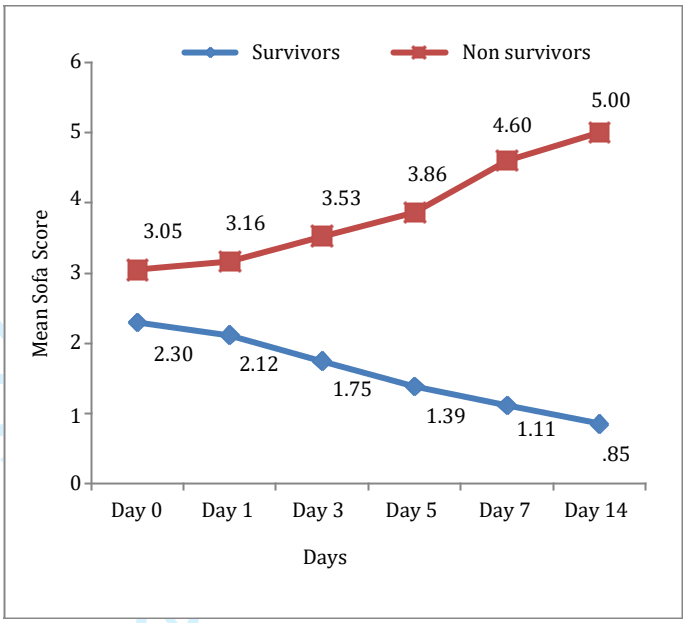

Figure 1: Line graph for SOFA score showing difference between survivors and non survivors

Figure showing serial Sequential Organ Failure Assessment (SOFA) score among survivors and non-survivors. Increasing SOFA score was associated with mortality. The mean SOFA score at day 0 was 2•30 and 3•05 for survivors and non-survivors respectively. The difference in the SOFA score showed divergence between the two groups over time.

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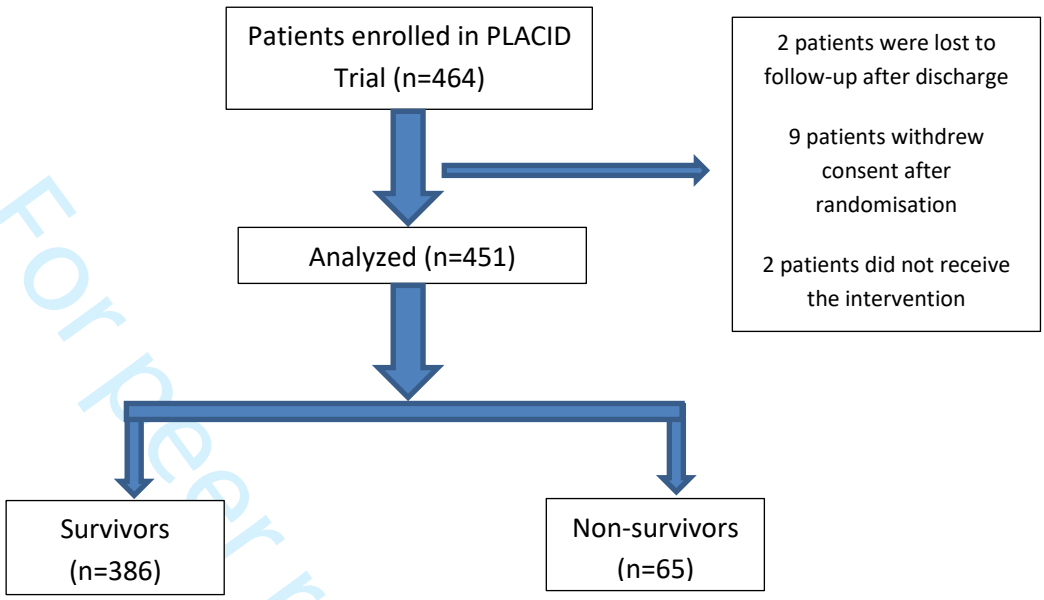
Supplementary

Flowchart for the study protocol



The Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease (PLACID) Trial recruited 464 eligible patients for the study. The primary outcome at 28 days was not available for two patients who were lost to follow-up after discharge; nine patients withdrew consent after randomisation and two patients did not receive the intervention after randomisation as a matched donor was not available. The cohort with known outcome at 28 days thus comprised of 451 patients out of whom 386 survived and 65 died.

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Factors associated with mortality among moderate and severe COVID 19 patients in India: A secondary analysis of a Randomised Controlled Trial

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Primary Subject	Public health

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Factors associated with mortality among moderate and severe COVID 19 patients in India: A secondary analysis of a Randomised Controlled Trial

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Abstract

Objective:

Large data on the clinical characteristics and outcome of COVID-19 in the Indian population is scarce.We analysed the factors associated with mortality in a cohort of moderate and severely ill COVID-19 patients enrolled in a randomised trial on convalescent plasma.

Design:

Secondary analysis of data from a Phase II,Open Label, Randomised Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease (PLACID TRIAL).

Setting:

39 public and private hospitals across India, during the study period 22 April 2020 to 14 July 2020.

Participants:

Of the 464 patients recruited, two were lost to follow-up, nine withdrew consent and two patients did not receive the intervention after randomisation.The cohort of 451 participants with known outcome at 28-days was analysed.

Primary outcome measure:

Factors associated with all-cause mortality at 28-days post-enrolment.

Results:

The mean (SD) age was 51±12·4 years; 76·7% were males.Admission SOFA score was 2·4±1·1. Non-invasive ventilation, invasive ventilation and vasopressor therapy were required in 98·9%, 8·4% and 4·0% respectively.The 28-day mortality was 14·4%.Median time from symptom onset to hospital admission was similar in survivors (4 days;IQR 3-7) and non survivors (4 days;IQR 3-6).Patients with two or more co-morbidities had 2·25(95%CI:1·18–4·29,p=0·014) times risk of death.When compared with survivors, admission IL-6 levels were higher (p<0.001) in non-survivors and increased further on Day 3.On multivariable Fine and Gray model, severity of illness (sub-distribution hazard ratio (SHR)1·22,95%CI:1·11-1·35,p<0.001),PaO_2/FiO_2 ratio <100 (3·47,1·64-7·37,p=0·001),Neutrophil Lymphocyte ratio (NLR)>10(9·97,3·65-27.13,p<0·001), D-dimer >1·0mg/L(2·50,1·14-5·48,p=0·022),ferritin ≥500ng/mL(2·67,1·44-4·96,p=0·002) and LDH ≥450 IU/L (2·96,1·60-5·45,p=0·001) were significantly associated with death.

Conclusion:

In this cohort of moderate and severely ill COVID-19 patients, severity of illness, underlying co-morbidities and elevated levels of inflammatory markers were significantly associated with death.

PLACID TRIAL Mortality Assessment

Trial Registration:

CTRI/2020/04/024775

Article Summary

Strengths and limitations of this study

Strengths

There is no study from India, with representation from multiple states that has detailed the clinical profile and evaluated for factors associated with death. This study may help with strategic planning at a national level.

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the present analysis need not be adjusted for convalescent plasma intervention.

There may be variability of treatment provided in the multiple centres, however, care was taken that patients received best standard of care for COVID-19 dictated by the best available evidence at the time and guidelines for the management of COVID-19 issued by health authorities of the Indian government.

Limitations

The laboratory and biomarker assays for ferritin, lactate dehydrogenase, C reactive protein, and D-dimer were conducted using tests from different manufacturers.

Participants of this study may not comprise a true observational cohort as this was a *post hoc* analysis of a randomised control trial data. Our study did not analyse the effect of SARS-CoV-2 variants causing a high mortality in younger population during the second wave of COVID-19 infection, and therefore extrapolation to the general population must be carefully qualified.

Introduction

The first human case of Corona Virus Disease 19 (COVID-19) caused by the novel coronavirus (named Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2) was reported in Wuhan City, China in December 2019. On 30 January 2020, the World Health Organisation (WHO) declared that the outbreak of COVID-19 constituted a Public Health Emergency of International Concern (1). Based on the high level of global spread and the severity of COVID-19, on 11 March 2020, the Director-General of the WHO declared the COVID-19 outbreak a pandemic (2). The sudden outbreak followed by rapid spread in a globalised world, resulted in a huge burden on the healthcare system, besides affecting the socio-economic well-being among all nations.

In India, the disease was first detected on 30 January 2020 in the state of Kerala, in a student who returned from Wuhan (3,4). After a brief, initial respite, the virus spread at a rapid pace in India, resulting in more than 10 million confirmed cases as of December, 2020 with more than 145,000 deaths (5).

Most patients diagnosed with COVID-19 experience mild to moderate respiratory illness, fever, dry cough and fatigue and recover without requiring special treatment (6). Oxygen desaturation is the hallmark of progression. Patients with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. These patients may develop viral pneumonia, with resultant dyspnoea and hypoxaemia which may progress to respiratory or multi- system failure and even death (7). There is paucity of large-scale data on the clinical characteristics, outcomes of COVID-19 in the Indian population and evaluation of risk factors with an unfavourable outcome at a national level. Identification of such potential risk factors is important to anticipate medical treatment and to reduce the mortality burden for severe COVID-19 illness by proactive interventions.

The Indian Council of Medical Research (ICMR) conducted a randomised trial (A Phase II, Open Label, Randomised Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease, PLACID TRIAL) to determine the effectiveness and safety of convalescent plasma in patients with moderate and severely ill COVID-19 to limit progression of disease (8). Patients received standard of care for COVID-19 in keeping with the institutional protocols, based on the best available evidence at the time and guidelines for the management of COVID-19 issued by national health authorities. Participants in the intervention arm received two doses of 200 mL of convalescent plasma, transfused 24 hours apart, in addition

to standard of care. The control arm did not receive any additional therapy. The study concluded that the use of convalescent plasma was not associated with a reduction in 28-day mortality (8).

The aim of this analysis was to identify risk factors associated with mortality by mining the data collected from the cohort enrolled in the PLACID TRIAL (8).

Methods

Participants

The study enrolled patients from 39 different hospitals, of which, 29 were teaching public hospitals and 10 were private facilities across 14 states and union territories. Patients over the age of 18 years who were confirmed to have COVID-19 based on a positive SARS-CoV-2 RT-PCR test and presenting with moderate and severely illness with either a partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200-300 or respiratory rate >24/min and decreased oxygen saturation on room air (SpO_2 < 93%) were included during the study period from 22 April to 14 July 2020. As per the guidelines issued by the Ministry of Health, Government of India at the time of conduct of the study, the subset of patients with the above criteria but with a respiratory rate between 24 and 30/min were classified as moderate disease. Those with respiratory rate >30 breaths/min were classified as severe disease (9). Patients were followed up for 28-days and assessed for their health status and all-cause mortality. Ethics approval was obtained from the ICMR Central Ethics Committee on Human Research (CECHR-002/2020) as well as from the Institutional Review Boards (IRB) / Institutional Ethics Committees of all the participating hospitals. Written consent was obtained from the patients or their families before enrolling in the study.

Data

Data was obtained from the ICMR PLACID TRIAL database collected in structured paper case record forms and entered in Research Electronic Data Capture system (REDCap, version 8·5 Vanderbilt University, TN). The trial protocol was registered with the Clinical Trial Registry of India (CTRI/2020/04/024775). After trial completion, based on co-operative agreement between the centres, and IRB permission, the data was shared and analysed further, to explore for other meaningful results. No separate ethical clearance was taken for this study.

PLACID TRIAL Mortality Assessment

Demographic, clinical, laboratory tests and outcome data were collected prospectively. Clinical symptoms, need for organ support (respiratory, renal, haemodynamic), laboratory tests (complete blood count, coagulation profile, serum biochemical profile, renal and liver function tests) were monitored serially on day of enrolment (day 0) and on days 1, 3, 5, 7, 14 and 28. Inflammatory biomarkers [lactate dehydrogenase (LDH), serum ferritin, and C-reactive protein (CRP)] were tested at admission and on day 3 and 7 whereas Interleukin 6 (IL-6) was done at admission and on day 3.

The outcome of interest was all-cause day 28 mortality. In addition, we looked for association between laboratory parameters and mortality.

Statistical Methods:

Mean and standard deviation (SD) or median and inter-quartile range (IQR) were used for continuous variables as appropriate, and for categorical variables, number and proportions were used. To find the association between mortality and study variables, Chi-square test/Fisher's exact test were used. To find the mean difference across the groups, independent t-test was used. Similarly, Mann Whitney U test was used to compare median difference. The primary end-point was all-cause mortality (event of interest) at day 28 from the time of enrolment, discharged alive (competing event) and hospital admission after day 28 (censored), whichever was earlier. Discharged alive was treated as a competing event because the event of "discharged alive" precludes the event of all-cause mortality. The variables that were statistically significant or clinically important were considered in the multivariable Fine and Gray regression model. However, if a variable was expected to have collinear concern or had sparse data, it was not included in the analysis. Two multivariable models were developed. The first model included clinical and laboratory parameters tested on day 0, 1, 3, 5, 7, 14 and 28 while the second included inflammatory biomarkers tested on day 0, 3 and 7, after adjusting for age and comorbidities. Variables that were considered included parameters that were strongly associated with mortality at univariate analysis or those known from previous literature to be strongly associated with outcome. For certain laboratory markers such as D-dimer, ferritin and LDH, clinically relevant thresholds were used for the analysis rather than using these data as continuous variables. The clinically relevant thresholds for these variables were set as >1.0 mg/L for D-dimer, ≥500 mg/mL for Ferritin and ≥450 IU/L for LDH. The threshold for Ferritin of 500 µg/L was based on the cut-off value for the diagnosis of Hemophagocytic lymphohistiocytosis (HLH) as well as some preliminary evidence in COVID that a

threshold of >500 µg/L was associated with invasive ventilator dependence (10). Similarly, traditionally a threshold of <0.5 mg/L is used to exclude pulmonary thromboembolism; in this context two thresholds were used, 0.5 to 1.0 mg/L and >1.0 mg/L (11). The model assumption was verified using log-log S (t) plots and Global test. A p-value of less than 0·05 levels was considered as statistically significant. All statistical analysis were performed using STATA version 16·0 (StataCorp. 2019. College Station, TX).

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. The study results will be disseminated to the study participants via their treating doctors.

Results

The PLACID Trial recruited 464 eligible patients for the study. The primary outcome at 28-days was not available for two patients who were lost to follow-up after discharge; nine patients withdrew consent after randomisation and two patients did not receive the intervention after randomisation as a matched donor was not available. The cohort with known outcome at 28 days thus comprised 451 patients (*supplementary*).

The primary outcome of the PLACID TRIAL, disease progression or all-cause mortality at day 28, did not differ across the trial arms, therefore the analysis did not adjust for convalescent plasma intervention. The distribution of patients in the intervention and control arms were 50·3% (n=227) and 49·7% (n=224), respectively. The mean (SD) age of the cohort was 51 ± 12·4 years; 76·7% were males. Table 1 shows the distribution of demographic variables and clinical parameters in the study population.

The most common presenting symptoms were shortness of breath (91·6%), fatigue (78·7%), cough (68·5%) and fever (35%). Comorbidities were present in 59.9% of patients; 31.7% had any one comorbidity and 28·2% had two or more comorbidities. The most frequent comorbidities were diabetes (43·5%), hypertension (37·5%), obesity (6·9%) and Chronic Obstructive Pulmonary Disease (COPD) (3·3%). There was history of smoking in 8·2%. The time from onset of symptoms to admission was four days (IQR 3-7 days). Majority of the patients required non-invasive (98·9%) ventilatory support. The median duration of respiratory support was six days (IQR 4-10 days). In

this cohort, 4% patients required vasopressor support. None of the patients required Extra Corporeal Membrane Oxygenation (ECMO) or dialysis support.

The all-cause mortality at 28-days was 14·4% (95%CI: 11·5-17·9, n=65). Median time from symptom onset to hospital admission was four days in survivors (IQR 3-7 days) and non-survivors (IQR 3-6 days). The frequency of shortness of breath, cough and fatigue were similar in survivors and non-survivors; however, the presence of fever at admission was significantly (p=0·042) associated with death (table 1). Other than COPD and CKD (chronic kidney disease), other comorbidities were not significantly associated with death (table 1). Admission Sequential Organ Failure Assessment (SOFA) score was higher in non survivors. The need for invasive mechanical ventilation, duration of invasive mechanical ventilation and vasopressor therapy were associated with death (table 1).

On univariate analysis (table 2), there was an association between increasing age and mortality. Patients with two or more comorbidities had a 2·25 (95%CI: 1·18-4·29, p=0·014) times increased chance of mortality. There was a strong mortality association for platelet count <100 * 10^9/L (SHR 6·88, 95%CI: 3·61-13·13, p<0·001), neutrophil lymphocyte ratio (NLR) >10 (28.84, 11·92-69.76, p<0·001), LDH ≥450 IU/L (4·88, 2·72-8·75, p<0·001), D-dimer >1mg/L (3·34, 1·55-7·19, p=0·002) and ferritin ≥500ng/mL (4·11, 2·28-7·41, p<0·001). Admission IL-6 levels were significantly (p<0.001) higher (76.00, 18.27-171.77) in non-survivors than in survivors (18.51, 4.26-56.86). By day 3, IL-6 levels dropped to 11.6 (2.64-45.84) in survivors while it nearly doubled in non-survivors (140.35, 21.56-427.36). CRP did not show any statistical significance (1.0003, 0.999-1.001, p=0.080).

The need for invasive ventilation and vasopressors were associated with death (table 2). Increasing SOFA score was associated with mortality (1·63, 1·54-1·74, p<0·001). The mean SOFA score at day 0 was 2·30 and 3·05 for survivors and non-survivors respectively. The difference in the SOFA score progressively increased between the two groups over time (figure 1). Mortality also proportionately increased with lower PaO_2/FiO_2 values with sub-distribution hazard ratio (SHR) of 25.64 (14.8-44.41, p<0·001) in the severe group as compared to the mild group.

Two models were run for multivariable Fine and Gray regression model over a period of time (table 3). Model A included age, comorbidities, PaO_2/FiO_2, NLR and SOFA score. Model A revealed significant sub-distribution hazard ratios for PaO_2/FiO_2 ratio <100 (3·47, 1·64-7·37, p=0·001), NLR >10 (9·97, 3·65-27.13, p<0·001), SOFA score (1·22, 1·11- 1·35, p<0·001) after adjusting for age and

comorbidities. Model B included age, comorbidities, D-dimer, ferritin and LDH. D-dimer >1 mg/L (2·50, 1·14-5·48, p=0·022), ferritin ≥500 ng/mL (2·67, 1·44-4·96, p=0·002) and LDH ≥450 IU/L (2·96, 1·60-5·45, p=0·001), were associated with mortality after adjusting for age and comorbidities (table 3). IL-6 was omitted from the model as it was not measured on Day 7.

Discussion

In this study that enrolled patients in the PLACID trial from across India, SOFA score and clinical biomarkers like D-dimer, LDH and ferritin were identified as factors that could predict increased risk of death in moderate and severely ill COVID-19 patients. The definition of clinical grading of severity is different in India as compared to other countries (12–16). Mortality of critically ill COVID-19 patients varies significantly among already published case series and ranges from 16% to 78% (17–23). Two studies from Wuhan, which included moderate as well as critically ill patients, showed mortality rates of 3.77% and 14.14% (24,25). This wide variability can be explained by differences in the age of the population, distribution of risk factors, health system responses, varied treatment protocols and disparate follow-up times. In a series of critically ill patients in China, the 28-day ICU mortality was 61·5% (26). In a multicentric study from Italy, the mortality risk for patients without respiratory failure at admission was 1% after 15 days, while survival in patients with moderate-to-severe respiratory failure (PaO_2/FiO_2 ≤200 mm Hg) at admission was only 56% at 15 days (27). The fatality rate reported in Europe and the United States of America was significantly higher than in China (28). Therefore, findings obtained in a specific country might not be automatically extrapolated and national cohorts must be studied.

In our study population, mortality increased with age; this pattern was observed in other countries affected by COVID-19. Age seemed to affect the time from hospitalisation to death. Age-specific death rates were quite similar in studies from Asia, Europe and North America (29). In South Korea, Italy, France, Germany, England and Wales, and Spain, the COVID-19 attributed mortality rates rose by about 12% per year whereas the United States and Wuhan, China had a lower rate of increase of about 9·5% per year of age (30). In a meta-analysis of 611,583 subjects, the overall mortality was 12·10%; the lowest mortality rate was reported from China (3·1%) and the highest in the United Kingdom (20·8%) and New York State (20·99%). Among the patients included in the meta-analysis, 23·2% were ≥80 years of age; mortality was highest in these patients. The largest increase in

mortality risk was observed in patients aged 60 to 69 years as compared with those aged 50 to 59 years (odds ratio 3·13, 95% CI: 2·61-3·76) (31).

The presence of comorbidities significantly increases the death risk due to COVID-19. A higher risk of mortality was seen in our patients who had CKD and COPD. A meta-analysis, including 1389 COVID-19 patients, with 19·7% having severe disease showed a significant association of CKD with severe COVID-19 with pooled odds ratio as 3·03 (32). Similarly, the estimated mortality risk in patients with COPD was three times than those without (p<0·05) (33). We found that 43·5% of our patients had diabetes which is markedly higher when compared with patients from Korea which showed that 16·97% had diabetes mellitus (34). Our analysis showed that the presence of diabetes was not significantly different between survivors and non-survivors (42·5% vs. 49·2%, p=0·310), in contrast to the study from South Korea (34) which showed a much higher mortality among diabetic patients than in those without (20·0% vs. 4·8%). Hypertension and obesity were not significantly different among survivors and non-survivors in our study. However, the presence of two or more comorbidities was associated with mortality in our study.

The Fine-Gray model identified prognostic markers for mortality, most notably age ≥60 years, PaO_2/FiO_2 ratio <100, NLR >10, platelet count <100 x 10^9/L, ferritin >500ng/mL, LDH >450 IU/L and D-dimer >1mg/L. Our study findings were similar when compared with studies from Wuhan (35). Older age, leukocytosis, and high LDH level have been reported to be risk factors associated with in-hospital death in other studies also (36–38). IL-6 levels were significantly different in survivors and non-survivors at admission. By day 3 survivors had reducing IL-6 while it nearly doubled in non-survivors.

Mortality was higher amongst patients requiring invasive mechanical ventilation (SHR 19·57, 12.21-31.35, p<0.001) and those requiring vasopressors (SHR 11·36, 7.79-16.56, p<0.001). However, the median duration of invasive ventilation for survivors was 12 days (IQR 2, 14) and that for non-survivors was one day (IQR 1, 3). These results suggest that the sickest patients probably die very early in the course of hospitalisation, while patients with acute respiratory failure requiring ventilatory support may survive with prolonged ventilatory support. Therefore, invasive ventilation should be offered in a timely manner and effectively provided.

In our study, the SOFA score was recognised as a valuable tool that could be used to prognosticate outcome of patients with COVID-19. Competing risk regression models showed that the increase in

SOFA score was related to mortality, with a clearly divergent pattern between the two groups. Thus, an increasing SOFA score over time may be a factor that can be used to identify a subset of patients who may have an unfavourable outcome. Studies have shown that the SOFA score could be used to evaluate severity and 60-day mortality of COVID-19 with the optimal cut-off score of 5 (39).

The limitations of this study include, the variability of treatment provided in the multiple centres. The participants of this study may not comprise a true observational cohort, as this was a *post hoc* analysis of a randomised control trial data and extrapolation to the general population must be carefully qualified. Our study did not analyse the effect of SARS-CoV-2 variants causing a high mortality in younger population during the second wave of COVID-19 infection and this may limit generalisability of the data to the second wave. Despite these limitations, this study provides a comprehensive overview of prognostic factors in moderate and severely ill COVID-19 patients that included patients from across the country.

Conclusion

Older age, multiple comorbidities, low PaO2/FiO2 ratio and elevated levels of inflammatory markers are associated with worse prognosis. Serial SOFA score can be used for prognostication. Understanding the symptoms, burden of comorbidities and systematic monitoring of key laboratory parameters offer opportunities for targeted intervention in COVID-19 with the use of anti-inflammatory or immunomodulatory agents.

Figure legend

Figure 1 showing serial Sequential Organ Failure Assessment (SOFA) score among survivors and non-survivors. Increasing SOFA score was associated with mortality. The mean SOFA score at day 0 was 2•30 and 3•05 for survivors and non-survivors respectively. The difference in the SOFA score showed divergence between the two groups over time.

FOOTNOTES:

Authors Contributions:

Study design: JJM, LJ, JVP

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Clinical Management: SK, LT, AZ, JER, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG.

Data collection: JJM, SK, LT, AZ, AA, AM, GK, PC, TB, JER, PR, MM, BC, BL, SUB, VK, RD, JRK, RDS, BTC, SB, SD, ASU, AJJ, OS, VB, AB, PM, NS, MT, NMS, SPB, RSK, AG, DHR, KU, AJ, TCP, IN, PRJ, KVSB, CA, SJP, MN, MB, VKK, SMD, RVS, AS, JS, YAG, PDY, GS, HK, VSK.

Data Analysis: JJM, SK, LJ, TM, MJ, PR, MM, DD, JVP.

Data Interpretation: JJM, SK, AZ, LJ, JER, TM, MJ, DD, JVP

Manuscript writing: JJM, SK, LT, AZ, LJ, JER, BC, TM, MJ, PR, MM, DD, JVP, AA, AM, GK, HK, PC, TB

Study Administration: JJM, BC, JVP, AA, AM, GK, HK, PC, TB

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Data availability statement: Data will be made available, upon request, and must be accompanied by a brief proposal outlining the analysis plan. A signed data access agreement might be needed to ensure data safety and compliance with national rules about data sharing.

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Table 1: Distribution of demographic variables and clinical parameters in enrolled patients and comparison of survivors and non-survivors in the cohort

Variables		Overall (n=451) N (%)	Survivor (n=386) N (%)	Non survivor (n=65) N (%)	P value
Age (Mean ± SD)		51±12·4	50±12·4	56±11·3	**<0·001***
Age	**≤ 40**	104 (23·1)	97 (25·1)	7 (10·8)	**0·004**
	41-59	225 (49·9)	194 (50·3)	31 (47·7)	
	≥60	122 (27·1)	95 (24·6)	27 (41·5)	
Gender: Male		346 (76·7)	294(76·2)	52 (80·0)	0·499
Blood group	**A**	104(23·1)	91(23·6)	13(20·0)	0·518
	B	164(36·4)	140(36·3)	24(36·9)	
	AB	25(5·5)	19(4·9)	6(9·2)	
	O	158(35·0)	136(35·2)	22(33·8)	
History of smoking		37(8·2)	32(8·3)	5(7·7)	0·866
Comorbidities and Chronic illness					
Diabetes		196 (43·5)	164 (42·5)	32 (49·2)	0·310
Hypertension		169 (37·5)	139 (36·0)	30 (46·2)	0·118
Chronic obstructive pulmonary disease		15 (3·3)	10 (2·6)	5 (7·7)	**0·050**
Obesity ≥ 30		31 (6·9)	25 (6·5)	6 (9·2)	0·426
Chronic kidney disease		17 (3·8)	11 (2·8)	6 (9·2)	**0·024**
Coronary artery disease		31 (6·9)	23 (6·0)	8 (12·3)	0·106
Cerebrovascular disease		4 (0·9)	3 (0·8)	1 (1·5)	0·465
Symptoms at admission					
Shortness of breath		413 (91·6)	351 (90·9)	62 (95·4)	0·232
Fever		158 (35·0)	128 (33·2)	30 (46·2)	**0·042**
Cough		309 (68·5)	259 (67·1)	50 (76·9)	0·115
Fatigue		354 (78·7)	301 (78·2)	53 (81·5)	0·541
Severity of illness score					
SOFA score at admission*		2·40 ± 1·06	2·30±0·93	3·05±1·49	**<0·001**
Treatment					
Vasopressor		18 (4·0)	1 (0·3)	17 (26·6)	**<0·001**
Non-Invasive Ventilation (NIV)		446 (98·9)	383 (99·2)	63 (96·9)	0·101
Invasive ventilation		38 (8·4)	4 (1·04)	34 (52·31)	**<0·001**
Interval between symptoms onset to admission ǂ		4 (3, 7)	4 (3, 7)	4 (3, 6)	0·996
Duration of respiratory support days ǂ		6 (4, 10)	6 (4, 9·5)	6 (3, 10)	0·689
Duration of invasive ventilation days ǂ		1 (1,3)	12 (2, 14)	1 (1, 3)	**0·020**

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Duration of hospital stay days ǂ	14 (10, 18)	14 (11, 19)	8 (5, 14)	**<0·001**

ǂ Median (IQR) days in days – Mann Whitney U test was used
***Mean ± SD – Independent t test was used**

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Table 2: Univariate Fine and Gray model for baseline characteristics, laboratory parameters and inflammatory biomarkers

Variables		Univariate Analysis					
		Mortality			Discharged alive		
		SHR	95% CI	P value	SHR	95% CI	P value
Age	≤40	1·00			1·00		
	41-59	2.04	0.90 - 4.66	0.089	0.80	0.64 – 1.01	**0.057**
	≥60	3.51	1.53 - 8.07	**0.003**	0.56	0.42 - 0.73	**<0.001**
Gender	Male	1.19	0.64 - 2.19	0.582	0.87	0.70 - 1.09	0.228
Blood Group	O	1·00			1·00		
	A	0.94	0.48 - 1.87	0.866	0.89	0.69 - 1.15	0.389
	B	1.13	0.63 - 2.01	0.689	0.93	0.75 - 1.18	0.578
	AB	2.01	0.80 - 5.05	0.139	0.66	0.39 - 1.11	0.116
Comorbidities	No Comorbidities	1·00			1·00		
	1	1.62	0.82 - 3.21	0.166	0.79	0.63 - 0.99	**0.044**
	2 or More	2.25	1.18 - 4.29	**0.014**	0.70	0.55 - 0.88	**0.003**
Neutrophil/Lymphocyte ratio ǂ	<5	1·00			1·00		
	5-10	4.90	1.80 - 13.32	**0.002**	0.72	0.56 - 0.93	**0.013**
	>10	28.84	11.92 - 69.76	**<0.001**	0.17	0.12 - 0.26	**<0.001**
Platelet count ǂ **(* 10^9/L)**	<100	6.88	3.61 – 13.13	**<0.001**	0.16	0.05 - 0.49	**0.001**
	≥ 100	1·00			1·00		
SOFA score ǂ		1.63	1.54 - 1.74	**<0.001**	0.62	0.57 - 0.67	**<0.001**
D-dimer(mg/L) $	<0·5	1·00			1·00		
	0·5 - 1·0	1.53	0.63 - 3.67	0.346	0.82	0.64 - 1.06	0.129
	>1·0	3.34	1.55 - 7.19	**0.002**	0.57	0.45 - 0.73	**<0.001**
Ferritin(ng/mL) $	<500	1·00			1·00		
	≥500	4.11	2.28 - 7.41	**<0.001**	0.52	0.42 - 0.64	**<0.001**
CRP$ (mg/L)		1.0003	0.999 - 1.001	0.080	0.99	0.99 - 1.00	0.360
LDH$ (IU/L)	<450	1·00			1·00		
	≥ 450	4.88	2.72 - 8.75	**<0.001**	0.53	0.43 - 0.66	**<0.001**
PaO2/FiO2ǂ	<100 (severe)	25.64	14.8 - 44.41	**<0.001**	6.5e-08	4.3e-08 - 9.9e-08	**<0.001**
	100-200(moderate)	5.97	3.05 - 11.69	**<0.001**	0.19	0.10 - 0.36	**<0.001**
	>200 (Mild)	1·00			1·00		
Interval from onset of symptoms to admission		1.05	0.96 - 1.14	0.334	0.97	0.94 - 1.00	0.058
Vasopressor support		11.36	7.79 - 16.56	**<0.001**	0.03	0.004 - 0.22	**0.001**
Invasive ventilation support		19.57	12.21 - 31.35	**<0.001**	0.01	0.002 - 0.09	**<0.001**

ǂ Laboratory Parameters were measured at day 0, 1,3,5,7 and day 14: $ inflammatory biomarkers values were measured at day 0, 3 and day 7.SHR: Sub-distribution Hazard ratio; CI: Confidence Interval

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Table 3: Multivariable Fine and Gray Model for baseline characteristics, laboratory parameters and inflammatory biomarkers

Variables		Multivariable Analysis (Model A)						Multivariable Analysis (Model B)					
		Mortality			Discharged alive			Mortality			Discharged alive		
		SHR	95% CI	P value	SHR	95% CI	P value	SHR	95% CI	P value	SHR	95% CI	P value
Age	≤40	1·00			1·00			1·00			1·00		
	41-59	1.23	0.60 - 2.49	0.572	1.03	0.81 - 1.32	0.825	1.55	0.65 - 3.71	0.325	0.95	0.74 - 1.21	0.671
	≥60	1.44	0.67 - 3.09	0.347	0.94	0.70 - 1.26	0.675	1.72	0.67 - 4.46	0.261	0.78	0.57 - 1.06	0.110
Comorbidities	No Comorbidities	1·00			1·00			1·00			1·00		
	1	1.20	0.69 - 2.10	0.515	0.91	0.72 - 1.14	0.407	1.31	0.59 - 2.91	0.509	0.87	0.67 - 1.11	0.254
	2 or More	1.76	1.02 - 3.03	**0.041**	0.89	0.69 - 1.14	0.329	2.68	1.26 - 5.70	**0.011**	0.69	0.52 - 0.93	**0.014**
Neutrophil/Lymphocyte ratio ǂ	<5	1·00			1·00								
	5-10	3.34	1.21 - 9.19	**0.020**	0.81	0.64 - 1.03	0.095						
	>10	9.97	3.65 - 27.13	**<0.001**	0.39	0.26 - 0.58	**<0.001**						
SOFA score ǂ		1.22	1.11 - 1.35	**<0.001**	0.75	0.68 - 0.83	**<0.001**						
D-dimer(mg/L) $	<0·5							1.00					
	0·5 - 1·0							1.29	0.54 - 3.10	0.565	0.84	0.65 - 1.09	0.198
	>1·0							2.50	1.14 - 5.48	**0.022**	0.64	0.49 - 0.82	**<0.001**
Ferritin(ng/mL) $	<500							1·00			1·00		
	≥500							2.67	1.44 - 4.96	**0.002**	0.69	0.55 - 0.86	**0.001**
LDH$ (IU/L)	<450							1·00			1·00		
	≥ 450							2.96	1.60 - 5.45	**0.001**	0.68	0.55 - 0.85	**0.001**
PaO2/FiO2ǂ	<100 (severe)	3.47	1.64 - 7.37	**0.001**	3.1e-07	1.7e-07 - 5.7e-07	**<0.001**						
	100-200(moderate)	1.91	0.91 - 4.004	0.087	0.401	0.19 - 0.85	**0.016**						
	>200 (Mild)	1·00			1·00								

ǂ Laboratory Parameters were measured at day 0, 1,3,5,7 and day 14: $ Inflammatory biomarkers values were measured at day 0, 3 and day 7

(Model A) Multivariable Fine and Gray model for Age, comorbidities with Laboratory Parameters, (Model B) Multivariable Fine and Gray model for Age, comorbidities with inflammatory biomarker values
SHR: Sub-distribution Hazard ratio; CI: Confidence Interval

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Figure 1:

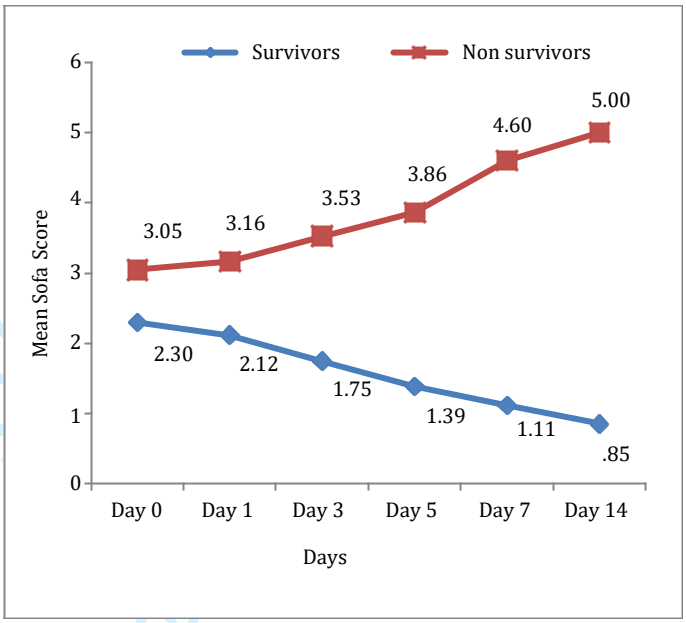

Figure 1: Line graph for SOFA score showing difference between survivors and non survivors

Figure showing serial Sequential Organ Failure Assessment (SOFA) score among survivors and non-survivors. Increasing SOFA score was associated with mortality. The mean SOFA score at day 0 was 2•30 and 3•05 for survivors and non-survivors respectively. The difference in the SOFA score showed divergence between the two groups over time.

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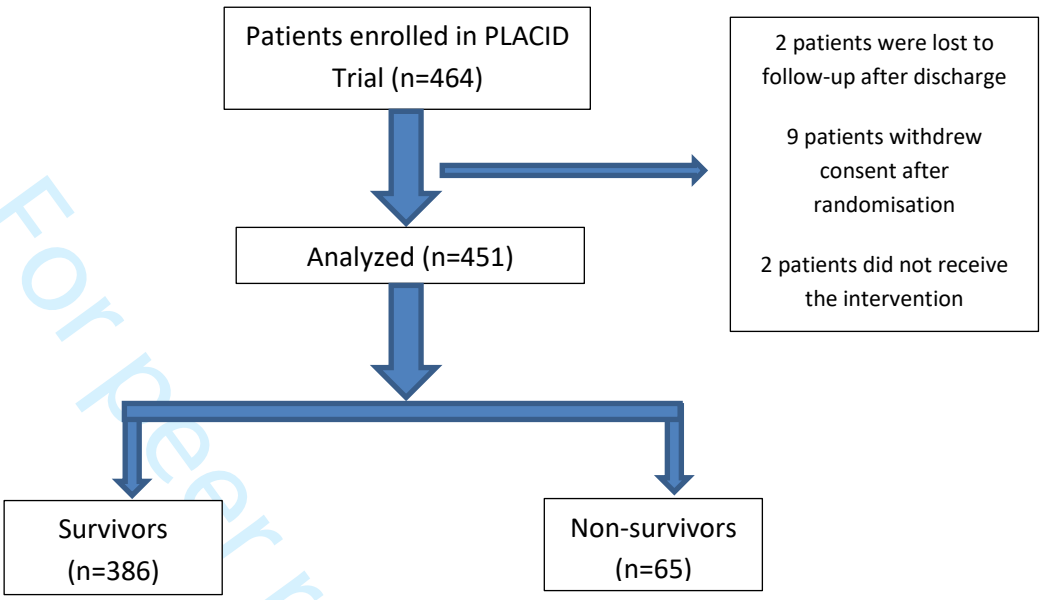
Supplementary

Flowchart for the study protocol



The Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease (PLACID) Trial recruited 464 eligible patients for the study. The primary outcome at 28 days was not available for two patients who were lost to follow-up after discharge; nine patients withdrew consent after randomisation and two patients did not receive the intervention after randomisation as a matched donor was not available. The cohort with known outcome at 28 days thus comprised of 451 patients out of whom 386 survived and 65 died.